THE YEAR BOOK *of* MEDICINE

(1959 1960 YEAR BOOK *Series)*

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DEPARTMENTS *of the* YEAR BOOK *of* MEDICINE

Infections

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The Chest

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TABLE OF CONTENTS

The designation (1959 1960 Series) used on the cover and title page of this volume is to indicate its publication during the series year which begins in September 1959

PART I

INFECTIONS

PART II

THE CHEST

PART III

THE BLOOD AND BLOOD FORMING ORGANS

PART IV

THE HEART AND BLOOD VESSELS AND THE KIDNEY

PART V

THE DIGESTIVE SYSTEM

PART VI

METABOLISM

INFECTIONS

PAUL B BEESON M D

PART I

INFECTIONS

BASIC INVESTIGATIONS

State of Lymphatic Capillaries in Acute Inflammatory Lesions A A Miles and Ellen M Miles[1] (Lister Inst of Preventive Medicine London) tested the validity of Menkin s hypothesis of lymphatic blockade as a defense against the spread of local infections which postulates that occlusive thrombi are produced in the lymphatic capillaries draining the infected region as part of the tissue reaction to a pathogen The lymphatic plexus in the skin of the guinea pig s ear like that in the mouse s ear is readily studied by the technic of microinjection of dyes and opaque inks

Inflammatory reactions 1 9 days old to intracutaneous turpentine Proteus vulgaris endotoxin Corynebacterium diphtheriae toxin and Clostridium welchii alpha toxin and to living Cl welchii Staphylococcus aureus and a pyogenic coccobacillus were investigated in the ear of the mouse and 1 day old reactions to Staph aureus and Streptococcus pyogenes in the ear of the guinea pig

Occlusion of the lymphatic plexus occurred at the center of most of these mature lesions but the area of the occluded plexus seldom exceeded 25% of the total area of pronounced inflammation and in many cases was below 10% Only lymphatic channels traversing regions undergoing coagulative necrosis were blocked

In mature staphylococcic abscesses in the skin of the guinea pig s ear abundant living cocci were demonstrated in inflamed tissue well outside the central area of lymphatic occlusion

In lesions made by doses of staphylococci or streptococci that at 24 hours would induce occlusion no lymphatic occlusion was observable 5 hours after infection i e at the end of the decisive period during which the maximum size of the

(1) J P th & B t 76 21 35 J ly 1958

local lesion and degree of systemic generalization of the infection are largely determined

(The evidence contradicts the hypothesis of lymphatic blockade as an effective defense mechanism in the decisive stages of reaction to primary lodgment of bacteria if the blockade is understood to be an obstruction to the movement of pathogens from a local lesion to the lymph glands interposed between the glands and actively infected tissues The trapping of living pathogens in the central region of an infective focus where lymphatic occlusion occurs as part of a generalized coagulative necrosis of the tissues may have some defensive value but the lymphatic events in such a region do not constitute a blockade

► [Here we have a careful and convincing study of some of the factors which tend to limit the spread of micro-organisms in an acute inflammatory process The conclusion that lymphatic blockade plays a comparatively minor role is in conflict with the viewpoint long advocated by Menkin and now widely quoted in textbooks of pathology—Ed] (

Role of Endogenous Pyrogen in Genesis of Fever is reviewed by W Barry Wood Jr [2] (Johns Hopkins Univ) As long ago as 1851 it was suggested that fever might be caused by products of inflammatory lesions In 1943 a pyrogenic euglobulin fraction later called pyrexin was separated from inflammatory exudates by Menkin It was heat stable and even when boiled retained its full activity resembling bacterial pyrogens in this respect Subsequent studies indicated that pyrexin has many of the other properties of pyrogenic bacterial endotoxins In 1948 a fever producing substance with very different properties was extracted from polymorphonuclear leukocytes Each of the characteristic properties of pyrexin is common to bacterial pyrogens but none of these properties is found in the leukocyte pyrogen

A study (1953) on the pyrexial response of rabbits to typhoid vaccine revealed that as long as 3 hours after injection the serum contained a component which produced fever when injected intravenously into a second set of rabbits This transferable pyrogen was later shown to be separate from bacterial endotoxin The newly discovered factor appeared to be endogenous and was biologically indistinguishable from leukocytic pyrogen

(These findings plus the fact that bacterial endotoxins have an affinity and toxicity for leukocytes suggest that

(2) Lancet 2 53 56 July 12 1958

endotoxin induced fever is due to activation of thermoregulatory centers of the brain by circulating endogenous pyrogen released from leukocytes injured by the endotoxin The relatively long latent period and postinjection leukopenia regularly observed in endotoxin fever strengthen this hypothesis)

/ The conclusion appears justified that the fever of most if not all acute bacterial infections which cause a predominantly granulocytic exudate and do not directly involve the central nervous system is due to a common factor—a circulating endogenous pyrogen derived from polymorphonuclear leukocytes and analogous to the blood borne substance found in the serum of rabbits with pneumococcic peritonitis and streptococcic cellulitis /

The febrile response to intravenous influenzal virus is directly related to the presence of a circulating endogenous pyrogen which is indistinguishable from a leukocytic pyrogen It is yet undetermined as to whether this factor is derived from polymorphonulear leukocytes or from some other cellular source A similar substance has been found in the blood stream of animals with fever induced by tuberculin hypersensitivity (These observations constitute additional evidence that endogenous pyrogens derived from inflammatory exudates play a central role in the pathogenesis of many forms of fever/

Two major problems remain unsolved the chemical identity of the leukocytic pyrogen and the possibility that cells other than polymorphonuclear leukocytes may be able to elaborate a similar if not identical fever producing factor

► [This article presents evidence which conflicts with another of Menkin's claims that pyrexin is the substance produced by acute inflammation which causes fever in the host animal Careful reading of Menkin's reports reveals little evidence that during the isolation and characterization of pyrexin he was aware of or took precautions to avoid the danger that his materials might become contaminated by bacterial pyrogens The latter are ubiquitous and are themselves potent causes of fever This technical problem has greatly handicapped all other workers who have attempted to determine the nature of the endogenous fever producing substances —Ed]

Concerning the Nature of Properdin System Ralph J Wedgwood[3] (Western Reserve Univ) points out that specific serologic factors (classic antibodies) are only one segment of the general phenomenon of serologic resistance to

(3) Ped tri 22 991 1000 N mbe 1958

infection Recent emphasis has changed from specific immunity to natural resistance The properdin system is one non specific mechanism that appears to be involved in natural resistance When zymosan is incubated in human serum at 37 C the third component of complement is inactivated This does not occur at 15 C At this temperature the zymosan combines with a serum protein (properdin) essential for the inactivation The protein can be eluted from zymosan It was designated properdin from the Latin *pro* and *perdere* (meaning to prepare to destroy) Properdin appears to be a beta globulin with an isoelectric point at about pH 5 6 and a molecular weight of about 1 000 000

The properdin system (properdin complement and magnesium) has various biologic activities destruction of certain bacteria inactivation of some animal and bacterial viruses lysis of abnormal erythrocytes (from patients with paroxysmal nocturnal hemoglobulinuria or treated with tannic acid or basic polypeptides) and the killing of a protozoan (Toxoplasma gondii)

The author believes it is unlikely that a system such as the properdin which can lyse bacteria and inactivate viruses would exist in serum without some biologic function Yet demonstration in vivo of the protective role of this or any other factor in serum is difficult

► [The existence of a previously unrecognized serum protein which seemed to participate in some of the phenomena of natural immunity was announced in 1954 and it was hailed at the time as an exciting discovery Much additional work has now been carried out with conflicting interpretation There exists a controversy as to the existence of properdin as a separate entity Here I have selected two differing points of view In the preceding article Wedgwood reviews much of the literature and inclines to the belief that there is such a thing as properdin and that it must have some function In the article which follows Nelson is skeptical and attempts to show that all of the actions attributed to properdin can be explained as a function of already known components of complement plus natural antibody This would be more satisfying if there were a little better agreement on what is meant by natural antibody At the very least this argument has had value in stimulating interest in the complex problem of natural resistance —Ed]

Alternative Mechanism for Properdin System is proposed by Robert A Nelson Jr [4] (Yale Univ) In 1954 experiments were described which indicated the presence in normal serum of a protein named properdin In later studies a basic role in varied areas of interest was ascribed to properdin such as in the mechanism of natural immunity

(4) J Exper Med 108 515 535 October 1958

against bacteria and viruses and for the defect in the immune mechanism after irradiation)

In view of the reactivity of properdin in various apparently unrelated phenomena a re examination of certain elementary aspects was undertaken Fixation of the components of complement in guinea pig serum was studied to learn the mechanism of inactivation of the third component by zymosan as compared with inactivation by certain classic antigen antibody complexes

Experiments with zymosan particles suggest that most serums from normal persons contain antibody which can sensitize zymosan to react in immune adherence immune aggregation and complement fixation Since this antibody exists in normal serum which is used as a source of complement the properties ascribed to properdin are in accord with the classic concept of antibody acting in conjunction with certain components of complement The chief characteristics of the properdin system can thus be explained without involving the concept of a new discrete entity

A clear definition of the nature of the substances involved in natural resistance is essential because of the varied and fundamental character of the phenomena under study(The properdin system has been implicated in observations extending from the neutralization of bacteriophage lysis of abnormal erythrocytes increased natural resistance to certain bacteria and resistance to malignancy) However the interpretation of the observed phenomena and the direction and emphasis of future research may be markedly influenced by the proposed concept that this mechanism involves natural antibody and complement components instead of a single and discrete new substance properdin

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SEPSIS AND SHOCK

Pseudomonas Septicemia Observations on 23 Cases seen during 1954 57 are presented by Claude E Forkner Jr Emil Frei III John H Edgcomb and John P Utz[5] (Nat l Inst of Health) The common clinical manifestations were

(5) Am J Med 25 877-889 December 1958



F g 1 (t p) —Clust r f cul l f om wh h Ps e g n w b t d n p e ltu e S ou d ng a how fl mm t
F g (bott m) —Shall w sh rply d m e t d a f g g ll l t d e to P rug n S rro nd g e s h w p rp d m lt pl p t h
(Court y of F k C E J t l Am J M d 25 877 889 D mbe 1958)

characteristic cutaneous lesions progressive jaundice neuro logic abnormalities arrhythmia ileus and sudden develop ment of hypotension

Skin lesions were seen in 9 (39%) patients There were four types of lesions (1) The most striking were those com

monly termed ecthyma gangraenosum which were characteristically round indurated ulcerated areas with black necrotic centers Some had rolled edges with a narrow erythematous zone surrounding the indurated central area Inflammatory reaction and pus formation were minimal These lesions varied in size and occurred most often in the anogenital area Except for the presence of bacteria clinically and histologically they resembled those of the Shwartzman reaction (2) There were vesicular lesions that tended to occur in clusters (Fig 1) Small blebs or vesicles appeared on an erythematous base and contained a cloudy opalescent fluid from which Pseudomonas aeruginosa could be cultured In contrast to the ecthymatous lesions these were inflamed and painful The vesicles eventually ruptured then assumed an ecthymatous appearance or healed completely (3) There were lesions that appeared as a flat sharply demarcated cellulitis which enlarged rapidly and became hemorrhagic and necrotic (Fig 2) Such areas were usually not painful (4) There were small pink round or oval maculopapular plaques or nodules characteristically found on the trunk These measured less than 2 cm in greatest diameter were symptom free and appeared before positive blood cultures were obtained

All but 1 patient died Median duration of life after the first positive blood culture was 4 days Microscopic morphologic changes of primary and secondary pseudomonas lesions indicated great affinity of this micro organism for the walls of small vessels The second commonest cause of septicemia and the commonest bacterial cause of death among patients with leukemia was Ps aeruginosa

Shock in Sepsis Clare G Peterson and William W Krippaehne[6] review data on 202 patients who died on the University of Oregon surgical service Of these 68 were classed as deaths in sepsis though it is seldom possible to connect fatality with infection alone

The triad of sepsis shock and hyperthermia was common Bacteremia septicemia and metastatic phenomena were often present The bacteria were predominantly Staphylococcus aureus streptococci Escherichia coli Pseudomonas aeruginosa Proteus vulgaris and Aerobacter aerogenes

In treatment trial with a vasopressor is indicated Be

(6) Am J Surg 96 158 171 Aug 1958



Fg 1 (t p) —Cl t f l e les f m wh h P rug n w b t d p e e ltu e. S nd g eas sh w fl mm t

Fg 2 (bottom) —Sh ll w h ply d m cat d f g g e ll l t s d e to P ruginosa S d g e h w p rp d m lt pl p t h (C rt y of Fo k C E J t J Am. J Med 25 877 889 D mb 19 8)

characteristic cutaneous lesions progressive jaundice neurologic abnormalities arrhythmia ileus and sudden development of hypotension

Skin lesions were seen in 9 (39%) patients There were four types of lesions (1) The most striking were those com

known endotoxin Therefore there is reason to believe that an endotoxin may be involved in the death from traumatic shock

The authors previously demonstrated a toxin in the blood of over 80% of dogs and rabbits in advanced hemorrhagic shock This toxin was revealed by use of a rabbit that had been exposed to hemorrhagic shock for 90 minutes Such an animal s defenses are down because it succumbs to 10^{-6} mg Escherichia coli endotoxin which in the normal rabbit has an M L D 100 of 10^{-1} mg The animal also dies if transfused with blood from an animal dying of hemorrhagic shock If the rabbit is transfused with its own shed blood or with blood from a normal rabbit it perks up quickly and within a few hours behaves like a normal rabbit recovering completely if not further molested

If the toxin is bacterial endotoxin the toxic plasma or lipopolysaccharide extract should possess all the known biologic properties of bacterial endotoxins The toxin should produce hemorrhagic necrosis of the intestinal mucosa or focal hemorrhages in the wall of the gut or both pyrogen response leukopenia in a normal recipient and the generalized Shwartzman reaction If given intravenously for 5 6 days to normal rabbits the toxin should like known endotoxins induce resistance to a lethal dose of endotoxin Except for as yet only tentative evidence that shock plasma induces resistance to a lethal dose of endotoxin shock plasma possesses all these properties whereas normal plasma pos esses none of them All the chemical biologic and pharmacologic data suggest that the toxin is an endotoxin

It is believed that in the normal animal endotoxins are constantly entering the circulation from the intestine presumably in not more than trace quantities ready to produce vascular collapse the moment the endotoxin detoxifying potential of the reticuloendothelial system is destroyed by any agent capable of doing so When traumatic shock however produced becomes unresponsive to therapy the refractory state of the peripheral vessels is due to unneutralized endotoxins

► [Fine and his associates are here reviewing a long series of experiments which they have conducted and which seem to fit nicely with their hypothesis that irreversible shock is associated with an inability to dispose of toxic bacterial products formed in the intestine —Ed]

cause therapy must be prolonged relatively high concentrations in small volumes of solution are indicated to minimize vascular overloading A 24 mg/L norepinephrine concentration and 100 mg/L Neo Synephrine® concentration are possible Norepinephrine infusions cause intense local vasoconstriction and may damage the tissues Therefore initial vasopressor therapy has been with Neo Synephrine® reserving norepinephrine for those who do not respond satisfactorily

Irreversible structural damage by hemorrhage into the adrenals during shock and sepsis was seen in the patient who died Definite pressor response will follow intravenous hydrocortisone within 15 30 minutes if adrenal insufficiency is a critical defect If sepsis shock and fever do not respond to blood replacement and vasopressors 100 mg [illegible] sone in 10% glucose solution with added saline [illegible] rational diagnostic therapeutic test

Persistent hyperthermia may lead to irreversible injury to the central nervous system liver and to circulatory collapse Therapy is directed toward rapid reduction of extreme temperature elevations to normal not to extreme hypothermia Supplemental oxygen is indicated Total body cooling leads to marked clinical improvement

Reversible pathology must be constantly sought At autopsy when the cause of death is found to be a missed abscess inadequately drained abscess continuing peritoneal contamination from necrosis and gangrene disruption of a suture line persistent ureteral obstruction as the cause of an overwhelming septicemia from fulminant pyelonephritis metastatic abscess that might have been drained unresolved atelectasis pneumonitis and multiple lung abscesses or space taking asphyxiating bilateral hydrothorax the lesson is bitter The first principle in treating hemorrhagic shock and shock in sepsis is never forget to treat the cause

Bacterial Factor in Traumatic Shock is evaluated by Jacob Fine Edward D Frank Herbert A Ravin Selma H Kutenberg and Fritz B Schweinburg[7] (Beth Israel Hosp Boston) A pathologic change characteristic of late shock is hemorrhagic necrosis of the intestinal mucosa or focal hemorrhages in the wall of the intestine or both This lesion is also characteristic of the animal killed by a lethal dose of [illegible]

(7) N[illegible]w E[illegible]gla[illegible]d J M[illegible]d 2[illegible]0 214 2[illegible]0 J[illegible] 29 1959

diseases Pathogenic micro-organisms were identified in only 23 of the cases but even among these there were 8 different species Thus no bacteriologic data are available on more than half of the patients treated. No follow up cultures are mentioned. The criteria for use of the terms cure and improved are not given. There is almost nothing in the report which provides a basis for comparison of the new agent with other antibiotics If this trial was done to compare the relative efficacy of tetracycline and tetracycline glucosamine it would have been advantageous to treat another series of patients matched according to age disease and infecting organism with tetracycline alone. Actually it is stated that 4 of the 50 patients in this series had previously received tetracycline and that improvement occurred only after tetracycline glucosamine therapy had been instituted. This must be accepted with caution since any second course of therapy is more likely to coincide with the natural tendency of infections to subside "Cure is credited to the drug in 5 persons who had infections by bacteria resistant to tetracycline This is in line with the general tenor of the article which tends to ascribe all improvement to the medicine given and to ignore the possible role of Mother Nature The fact is that the manifestations of incomplete abortion and postoperative wound infection (the two largest clinical groups in the series) can usually be expected to improve within a few days regardless of drug treatment. Presumably the u ual surgical measures to treat wound infections were used, although that is not stated.

For a sober appraisal of enhancing agents see the succeeding article which was published praise be as an editorial in that same journal. A well designed clinical trial is described later in this YEAR BOOK page 78 in an article on tetanus —Ed.]

Antibiotic Blood Level Enhancement. During the past year several papers have appeared purporting to show in man an enhancement of absorption of tetracycline by its use as a tetracycline phosphate complex or of various tetracycline antibiotics by their combination with various adjuvants Maxwell Finland[9] (Harvard Med School) carefully reviewed the data on which these claims were based and found the evidence unconvincing

The marked depressing effect of dicalcium phosphate on the blood levels of tetracycline has been demonstrated Calcium salts usually dicalcium phosphate are traditionally used by pharmacists as a filler in capsules of many drugs including antibiotics generally on the assumption that they are inert Therefore results that showed markedly improved blood concentrations with capsules containing the new enhancing agents were due largely to the depressing action of dicalcium phosphate in the control preparations

The confusion and conflicting claims are actually related to depressing rather than enhancing agents The products now available are improved over those of a year ago and have probably resulted more from subtraction than from

(9) A t b t c Med. & Cl The p 5 359 363 J 1958

Treatment of Gynecologic Infections with Glucosamine Potentiated Tetracycline A recent report indicates that oral administration of d glucosamine concurrently with tetracycline produces definitely higher antibiotic serum concentrations with an average enhancement of 105% after 2 hours over tetracycline given alone Martin L Stone Alexander Sedlis Joseph Bamford and William Bradley[8] (New York Med College) treated 50 gynecologic patients aged 21 59 with commercially prepared capsules containing 250 mg tetracycline hydrochloride and 250 mg glucosamine hydrochloride 1 capsule 4 times daily Diagnoses included incomplete abortion postoperative wound infection pelvic inflammatory disease pyelonephritis cystitis ectopic pregnancy endometritis and cervical carcinoma Pathogenic organisms were identified in 23 patients

Of the 50 patients 31 were considered cured and 13 improved but not cured 6 showed no response Organisms isolated from the 23 patients included Escherichia coli from 12 streptococci from 7 (beta streptococci from 2 and alpha streptococci Streptococcus faecalis Str durans an intermediate strain and an unidentified strain) Aerobacter aerogenes from 6 and Proteus mirabilis from 1

Eight strains were resistant to tetracycline 2 E coli and 1 each of alpha streptococci a gram positive cocci A aerogenes Str faecalis Str durans and P mirabilis However tetracycline glucosamine was administered to each of these patients to determine whether any increase in antimicrobial activity resulted from increased tetracycline levels Seven of the 8 responded to treatment and 5 were cured

► *[I selected for the lead off article in this section an example of the kind of clinical investigation which manufacturers often seem to rely on in their campaigns to sell us this or that antibiotic preparation The article is representative of many which appear every year especially in the journal from which it was taken It deals with the use of a new agent for enhancing the blood levels of tetracycline I doubt however that sound conclusions can be drawn from this kind of study A therapeutic trial should be conducted along the lines of any other scientific experiment using the most careful laboratory and clinical observations and incorporating standard methods of control Without that one is hardly justified in recommending the use of a therapeutic agent to the profession at large*

The 50 patients in this series were aged 21 59 and they had 8 diffe

(8) A t b t c Med & Cl n The p 5 3 327 M y 1958

well as in many acute and chronic urinary tract infections Chronic infections with pseudomonas enterococci and some proteus strains appear to be resistant In treatment of severe chronic and resistant tuberculosis kanamycin exerted some favorable effects but resistance to it developed rapidly

The major toxic effects are on the kidney and 8th cranial nerve Renal function impairment usually mild occurs in more than one fourth of the patients involves both glomerular and tubular function and probably is wholly or largely reversible When the underlying renal impairment is related to pyelonephritis it may actually improve if the treatment favorably influences the infection

Vestibular damage is rare but loss of hearing beginning in the high frequency range often occurs after subacute or chronic administration of effective doses especially with large doses and prolonged treatment

addition However many studies have shown that the new commercial preparations produce higher blood concentrations than the earlier ones even though the explanation of the mechanism of this improvement may have been in error Proof of superiority is open to question in many instances both statistically and because no essential supporting data about the tested products were included

All the presently available commercial tetracycline capsule preparation whether they contain citric acid glucosamine sodium hexametaphosphate or phosphate complex produce for all practical purposes blood levels in man of about the same order of magnitude Certainly no clinically significant differences are obtained after administration of these products in comparable dosages

Kanamycin an antibiotic closely related to neomycin is described by Maxwell Finland[1] (Harvard Med School) It consists of 2 amino sugars linked glycosidally to 2 desoxystreptamine

In vitro kanamycin is highly or moderately active against many common pathogenic aerobic gram positive and gram negative bacteria and mycobacteria but some pneumococci most streptococci pseudomonas anaerobic organisms yeasts and fungi are nearly all highly resistant Its activity against pathogenic staphylococci parallels closely that of neomycin and paramomycin Resistance to kanamycin can be readily induced in staphylococci and in Escherichia coli This is accompanied by complete cross resistance to neomycin and paramomycin and partial cross resistance to streptomycin and certain other related antibiotics but no cross resistance to any of the other antibiotics that are generally available

In the usual laboratory animals kanamycin has shown relatively low acute toxicity Absorption and excretion from subcutaneous and intramuscular doses in animals and from intramuscular doses in man is rapid Intramuscular doses must be given at 6 hour intervals to maintain adequate therapeutic levels except for doses of 1 Gm which may be given at 8 or 12 hour intervals Orally it is poorly absorbed

Clinical results with intramuscular use of kanamycin were highly satisfactory in many staphylococcic infections even when the organisms were resistant to other antibiotics particularly penicillin streptomycin and the tetracyclines as

(1) La[illegible] 07 11 July [illegible] 1958

which had been largely banished by penicillin have returned It is probably only a matter of time until penicillin resistance will be met on an increasing scale all over the world Further careful and prolonged follow up will be necessary In all likelihood various types of provocative tests will again have to be performed to ascertain cure

► [Gloomy prediction but see next article—Ed.]

Sensitivity of Strains of Gonococci to Penicillin Sulfathiazole and Streptomycin J L Cradock Watson R A Shooter and C S Nicol[6] obtained cultures from all men with gonorrhea who attended the venereal disease departments of St Thomas s and St Bartholomew s hospitals London during 5 months Cultures were also collected from the women contacts when they attended Satisfactory cultures were obtained from 200 of 295 patients A further 11 cultures were obtained from 10 of these 200 patients who had a recurrence Of the 200 patients 190 were men Four of the women s contacts were among the 190 men

At both hospitals routine treatment for gonorrhea is a single intramuscular dose of 300 000 units of procaine penicillin which was given to 190 patients Gonorrhea recurred in 25 All had received the routine treatment except 1 who had been given 600 000 units

Laboratory sensitivity tests were done by incubating the gonococci anaerobically in chocolate agar plates containing serial dilutions of the three antibiotics These tests showed that 38 of the strains obtained from the 200 patients required 0 128 unit/ml or more for inhibition and 5 needed 0 512 unit The clinical course of patients infected with these strains suggested that the increased in vitro resistance to penicillin might be reflected in the results of treatment with conventional doses If the possibility of reinfection is discounted 13 (34%) of the 38 patients infected with resistant strains relapsed as opposed to only 12 (7%) of the 162 patients who were infected with sensitive strains

The over all cure rate of 87 5% using 300 000 units of procaine penicillin is acceptable But in view of the experience in this series the future dosage will be increased to 600 000 units of penicillin and patients with clinical relapse will be treated with streptomycin and sulfonamides

(6) Brit M J 1 1091 1092 May 10 1958

The data suggest that specific treatment reduces the carrier rate somewhat but this has not been proved

► [The figures on the effect of chloramphenicol in acute illness are more interesting than those on the incidence of carriers —Ed]

Failure of Penicillin in Treatment of Acute Gonorrhea in American Troops in Korea was studied by Ernst Epstein[5] The remarkable response of gonorrhea to penicillin has long been emphasized and it is usually held that penicillin resistant Neisseria gonorrhoeae do not appear However in Korea failure of gonorrhea to respond to adequate penicillin treatment is not uncommon Frequently military physicians in Korea encounter in soldiers acute gonorrhea that persists despite 5 or even 10 daily injections of 600 000 units of aqueous solution of procaine penicillin G

Of 148 men with acute gonorrhea given 5 daily intramuscular injections of 600 000 units of procaine penicillin G treatment failed in 30 In 13 of these a second course was given It was successful in 9 and in the 4 failures cure was obtained with oxytetracycline In 17 others in whom the initial course of penicillin failed oxytetracycline treatment was successful in 15 In the 2 who were not cured chloramphenicol treatment was successful The present high rate of failure with repeated doses is in marked contrast to the much lower rate of failure with single smaller doses reported elsewhere 2 years ago

Reinfection cannot possibly explain treatment failures in patients in whom N gonorrhoeae was demonstrated in the discharge while the patient was on penicillin treatment The daily dose of penicillin used is several times as great as the amount needed for effective prophylaxis of gonorrhea

Although many authorities recommend treatment of acute gonorrhea in the male with a single injection of 600 000 units of repository penicillin this has been abandoned by most military physicians in Korea Epstein found procaine penicillin G in oil with 2% aluminum monostearate disappointing Not only are treatment failures more common but the clinical picture is obscured by the more prolonged suppressing action of the repository form of penicillin

Emergence of penicillin resistant strains of N gonorrhoeae has grave significance The twin problems of chronic gonorrhea in the male and the asymptomatic male carrier

(5) J A M A 169 1055 1059 Mar 7 1959

which had been largely banished by penicillin have returned It is probably only a matter of time until penicillin resistance will be met on an increasing scale all over the world Further careful and prolonged follow up will be necessary In all likelihood various types of provocative tests will again have to be performed to ascertain cure

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(6) Brit M J 1 1091 109 May 10 1958

PROBLEM OF STAPHYLOCOCCIC INFECTIONS

Observations on Nature of Staphylococcic Infections David E Rogers[7] (New York Hosp Cornell Med Center) studied the ways in which host tissues deal with experimentally induced staphylococcic infections He observed in previous studies that despite the fact that virtually all staphylococci were ingested by leukocytes in human beings little or no killing of staphylococci could be detected Subsequent studies indicated that certain staphylococci could survive for long periods within human and rabbit polymorphonuclear leukocytes and that this ability correlated well with human or animal pathogenicity

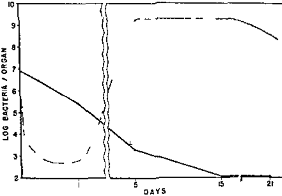
To appreciably affect intracellular staphylococci 50 200 times the amount of penicillin or streptomycin necessary to kill extracellular staphylococci is required Thus incorporation within cells appears to protect the staphylococcus It also seems that staphylococci are metabolically less active within cells and that this sluggishness conditions their susceptibility to antimicrobial drugs Staphylococci surviving within polymorphonuclear leukocytes may also play a role in their persistence within the blood stream The ability of staphylococci to survive phagocytosis may protect them from antimicrobial drugs present in extracellular fluids When injected into the blood stream of animals the bulk of the staphylococci is rapidly sequestered within the liver and spleen Subsequent multiplication however occurs primarily within the kidney Thus the paradox shown in Figure 3 takes place

Staphylococci persist at detectable levels for long periods in animals that survive their initial infection

Clinical and experimental experience indicates that microorganisms residing in staphylococcic abscesses are not destroyed by antibiotics regardless of their in vitro sensitivity This is not a problem of inadequate drug penetration into the abscess cavity

It is suspected that the focal abscess does not represent a good antigenic stimulus Fibrin membranes similar to th

(7) B H N w Y k A d Med. 35 25 38 J u y 19 9



F g 3—B h ıor f taphylococ n mous l d kıd eys aft nt eno ject n f ba te L t te n t lly h gh gg t g questration t c loe d th l l c ll T t f ll grad lly o 21 d y I cont ast k d y t te s ns p dly ft fi t 24 ho d m ın t t p g e l bsc f rma t on t ke pl (Courtesy f R g D E B ll. N w Y k Acad M d 35 25 38 Ja ry 1959)

membrane surroundıng the early abscess have been demon strated to operate as a selectıve filter passıng only certaın proteıns and other substances Endotoxın transfer across the abscess wall ıs sıgnıficantly modified

At New York Hospıtal over 95% of serıous progressıve staphylococcıc ınfectıons have arısen ın clınıcal sıtuatıons summarızed ın the table

INTRAHOSPITAL SITUATIONS IN WHICH STAPHYLOCOCCIC INFECTIONS COMMONLY ARISE

1 Patıents with probable systemıc alteratıons ın resıstance
   A Newborn ınfants
   B Patıents wıth leukemıa Hodgkın s dısease lupus erythematosus dıabetes renal faılure chronıc pulmonary dısease
2 Patıents wıth local alteratıons ın resıstance
   A Surgıcal procedures—major and mınor (ıncludıng tracheotomy urınary catheters venous cutdowns multıple ırrıtatıng ınjectıons)
   B Influenza exfolıatıve dermatıtıs burns
3 Patıents receıvıng certaın types of therapy
   (ACTH steroıds nıtrogen mustards purıne or folıc acıd antago nısts possıbly broad spectrum antıbıotıcs)

Staphylococcıc Infectıon ın Mothers and Infants Ma ternal Breast Abscesses and Antecedent Neonatal Sepsıs In an outbreak of staphylococcıc ınfectıon ın two maternıty unıts J A Monro and N P Markham[8] (Unıv of Otago)

(8) La t 2 186 190 J ly 6 1958

tound the responsible micro organism to be the staphylo coccus phage type 80/81 in each of 27 patients with breast abscesses

The infant was a frequent source of maternal infection and was usually contaminated directly or by aerial trans mission from staff carriers In the pathogenesis of breast abscess the transfer of staphylococci from infant to maternal breast milk is important

It was concluded that a nursery may be seeded with staph ylococci from a nasal carrier among the staff and a nursery reservoir of staphylococci may persist by hand or air trans fer from infant to infant An infant carrying staphylococci may transmit the organism to the mother s breast either di rectly via a cracked nipple or by inoculation of the breast milk and a breast abscess may develop

Puerperal Breast Abscess has usually been reported when there was seemingly a sudden outbreak or concentrated in crease in the number of cases C Otis Smith and Alexander Varga[9] studied the cases recorded over 10 years at Cook County Hospital and found only minor fluctuations in the incidence during 1945 53 but a marked increase in 1954 and 1955 Among 147 cases occurring from June to December 1955 symptoms appeared between 11 and 30 days post par tum in 104 (70 7%) In most cases at least a quarter segment of the breast both glandular and connective tissue was in volved whereas practically the whole breast was affected in more severe cases The commonest complaint was a painful lump or swollen breast Spontaneous rupture occurred in 10 cases before admission and bilateral involvement was found in 20

The sources of pathogenic bacteria causing breast abscess are manifold No one source can be incriminated exclusively Because of the widely varying sources regardless of the pa tient s environment it would be almost impossible not to be exposed to pathogenic staphylococci

Of 99 cultures obtained from breast ab cesses in different patients 96 were pure cultures and 3 mixed There were 59 pure cultures of coagulase positive hemolytic Staphylococcus aureus 36 of coagulase positive nonhemolytic Staph aureus

(9) Am J Obst & Gynec 74 1330 1341 Dec mbe 1957

and 1 of coagulase positive nonhemolytic Staph albus The coagulase positive hemolytic Staph aureus was moderately resistant or resistant to penicillin in 83% of specimens to tet racycline in 50% and to erythromycin in 77%

On admission the patients were given antibiotics Anal gesics were given for pain or discomfort If ready the ab scess was surgically drained the next morning The type of incision depends on the extent of the lesion If less than a quarter segment of the breast is involved circumareolar in cision suffices otherwise an extensive radial incision or multiple incisions if necessary should be used

Septic Thrombophlebitis with Septicemia Report of Three Cases Due to Staphylococcus Aureus Infection after Intravenous Use of Polyethylene Catheters for Parenteral Therapy is presented by R W Phillips and John D Eyre Jr[1] (VA Hosp Providence R I) Intravenous polyethy lene catheters have become increasingly popular for adminis tering solutions when long term parenteral therapy is needed

In each of the 3 patients the source of infection was septic phlebitis that developed at the site of a polyethylene cath eter In each the autoclaved plastic catheter had been in serted through a sterile large bore needle into the antecu bital vein the operator wearing sterile gloves and preparing the arm in the usual fashion with tincture of thimerosal The area had been covered with a dry sterile pad held in place with adhesive tape All 3 patients were seriously ill and debilitated when the complicating septicemia occurred Two had advanced Laennec s cirrhosis of the liver with bleeding varices and the other was receiving steroid therapy for advanced disseminated lupus erythematosus All there fore may be considered to have been in greater danger of acquiring infection with staphylococci Septic phlebitis de veloped after the plastic catheter had been in place for 4 5 and 7 days respectively In a previous study the fre quency of complications varied directly with the length of time the catheter was in place

Inspection of the site of catheter insertion reveals that after a few days the catheter does not fit tightly in the skin puncture and may slide back and forth as the patient moves

(1) N w E gland J M d 259 729 731 O t 9 1958

his arm in bed A small space around the catheter is common This is a source of contamination and a tract whereby micro organisms may enter the wound

Since the frequency of complications increases with duration of therapy through the catheter it should be removed as soon as practicable Use of a new site may be indicated after the catheter has been in place more than a few days Prophylactic antibiotic administration to prevent septic phlebitis is contraindicated because it does not prevent infection but results in infection with drug resistant organisms

► [This is now a well recognized risk and it hardly seems justifiable to continue use of plastic catheters for prolonged intravenous therapy It is probably safer to use needles and change the site of the drip every day or two —Ed]

Staphylococcic Parotitis This virulent and hitherto rare hospital acquired staphylococcic disease was observed by Robert G Petersdorf Ben R Forsyth and David Bernanke (Yale Univ) in 7 patients within 5 months Six of the 7 were elderly (table) and had severe debilitating chronic illnesses In only 3 was the parotitis intimately related to major surgery Dehydration seemed an important predisposing factor in 5 One patient had massive edema Clinically the condi

Clinical Data in 7 Pat

Case No	Age (Yr) & Sex	Underlying Disease	Status	Dehydration	[illegible]
1	76 (M)	Carcinoma of colon intestinal obstruction	Postop	Present	No
2	72 (F)	Cerebral hemorrhage	No op	Present	No
3	85 (M)	Generalized arteriosclerosis prostatic hypertrophy	Postop	Absent	No
4	50 (F)	Chronic relapsing pancreatitis	Remote op	Absent	No
5	81 (M)	Chronic pulmonary insufficiency pneumonia failure of left ventricle	No op	Present	Pr
6	83 (F)	Common duct stone cholangitis	Postop	Present	I r
7	84 (F)	Diabetes pyelonephritis	No op	Present	No

(2) New England J Med 259 1250 1254 Dec 25 1958

tion was characterized by sudden onset of a firm warm erythematous indurated swelling at the angle of the jaw and over the cheek associated with fever local pain and tenderness With external pressure pus exuded from the orifice of Stensen s duct Two patients died Both appeared to be improving until the on et of parotitis which was instrumental in their deaths The most notable laboratory abnormality was marked elevation in white blood cell count at the height of inflammation reaching a mean of 33 000

*Inspissated secretions may be important in the develop*ment of this infection but no stones were found in the ductal system of any of these patients Staphylococcic infection in other foci probably is unrelated to development of infection in the parotid gland Prophylaxis with antibiotics did not prevent development of this infection and in fact may have tended to favor the recurrence of infection by antibiotic resistant strains

Treatment depends on prompt administration of large doses of antibiotics to which the organism is sensitive Surgery is of little avail because the area can drain through Stensen s duct and the fibrous nature of the gland with its many septa interferes with proper external drainage

Staphylococcic Parotitis

	Wh e Cel C	T m			Du ov P D	Outcom
		X y	S g y	A t b ot		
4	Not done	Yes	No	Novobiocin	7	Infect subsided
2	26 000	No	No	Penicillin chloramphenicol & erythromycin	14	Infect. subsided
0	44 000	No	Yes	Vancomycin	14	Infect subsided
2	40 000	No	No	Penicillin & streptomycin	7	Infect. subsided
	19 000	No	No	Chloramphenicol	7	Infect subsided
6	33 000	Yes	Yes	Chloramphenicol & erythromycin	14	Patient died
0	34 600	No	No	Chloramphenicol & erythromycin	2	Patient died

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was 3 years) trauma to the back an unexplained pyrexial illness and tenderness of the spine When the subarachnoid space is tapped the likely finding is partial or complete spinal block with characteristic manometry and protein elevation

Treatment is immediate laminectomy evacuation of the abscess and tube drainage

► [Obviously the infant fell into good hands and the outcome was excellent Staphylococcic epidural abscess is a real emergency because irreversible damage to the spinal cord is likely to ensue if the abscess is not drained promptly If thought of a preoperative diagnosis can be made fairly definitely as in this case —Ed]

Hospital Laundry and Refuse Chutes as Source of Staphylococcic Cross Infection Valerie Hurst Moses Grossman Fred R Ingram and Alan E Lowe[4] (Univ of California) investigated the movement and staphylococcic contamination of the air of the laundry and refuse chutes in a modern 16-story hospital

Air flow studies showed considerable movement of air from the chutes into the hospital corridors This was strongest on the upper floors as much as 30 60 cu ft being released in the 5 10 seconds a chute door was opened for normal use All floors were subject to large gusts if the doors were open during the passage of materials down the chute

The air of the laundry chute contained 200-600 staphylococci/cu ft and the refuse chute up to 100 staphylococci/cu ft Lint in the laundry chute was heavily contaminated Most staphylococci were penicillin resistant and had group III phage patterns Many of the phage patterns were similar to those of staphylococci isolated from infected patients hospitalized at the time of the investigation It is probable that the staphylococci were deposited in the chutes by contaminated bedclothing and discarded infected refuse (surgical dressings swabs etc) Many patients acquired the infection in hospital and the chutes may have contributed to its spread

Hospital chutes should be designed to prevent the return of contaminated particles to hospital corridors and patient areas and materials from infected patients should not be placed directly into the chutes

Antibiotics for Staphylococcic Infections are evaluated by Maxwell Finland (Harvard Med School) It is not known whether there has actually been an increase in the incidence

(4) J A M A 167 1223 1229 July 5 1958
(5) M Cl North Am 42 1179 1194 September 1958

Acute Spinal Epidural Abscess Case in Infant with Recovery is reported by R G Rushworth and P B Martin[3] (London) As this condition is a neurosurgical emergency early diagnosis and prompt treatment are essential to prevent permanent cord damage Most reported cases have been in adults The present case illustrates the difficulty of diagnosis before neurologic signs appear

Boy born in April 1955 was hospitalized 15 months later He had been ill for 2 days and screamed whenever he was lifted by the arm pits or placed on his back On admission he was hot and fretful and in no great pain while lying quietly Two days after admission temperature rose to 103 F and respiration became more rapid The next day he began twitching and appeared about to have a convulsion Lumbar puncture showed clear fluid with 140 white cells/cu mm 91% polymorphonuclears 30 red cells/cu mm protein 300 mg/100 ml and sugar 83 mg/100 ml A blood culture taken at this time later grew Staphylococcus aureus

Infection was obviously present and despite the absence of focal signs a cerebral abscess had to be excluded Ventriculography excluded both a cerebral abscess and any other space occupying lesion Preliminary lumbar puncture again showed clear cerebrospinal fluid at a pressure of 30 mm Differential determination of the protein content indicated a cerebospinal fluid block Cisternal puncture and introduction of opaque dye revealed a block at the foramen magnum with only a thin stream descending to the 7th cervical vertebra where obstruction was complete Opaque dye introduced by lumbar puncture demonstrated complete obstruction at the 5th thoracic vertebra The myelographic appearances suggested an extradural lesion

Since the infant had had repeated staphylococcic infections the present pyrexial illness suggested epidural abscess as the most likely cause of the block Laminectomy was immediately performed A large collection of pus was found at the level of the 2d thoracic vertebra a drainage tube was inserted and the wound was closed Penicillin and streptomycin had been given before operation and these antibiotics were continued The organism was identified as a coagulase positive staphylococcus resistant to penicillin so this antibiotic was changed to oxytetracycline administered systemically Chloramphenicol was introduced locally via the drainage tube

After an initial rise in temperature to 104 F recovery was rapid and the wound healed perfectly No neurologic signs appeared and the infant began walking while in the hospital Systemic antibiotics were continued for 4 weeks and 6 weeks after operation he was discharged He has remained well during 15 months of follow up

The diagnostic features in this case were a history of infection weeks to months earlier (a study of 85 cases showed the average interval to be 4 2 weeks but in 1 case the interval

(3) A h D s Ch ldh od 33 61 264 Ju 1958

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and severity of these infections or whether the present concern about the staphylococcus is the result of increased awareness of a problem which has always existed The increasing use of bacteriology laboratories for identification of etiologic agents in severe infections and the general application of sensitivity tests have undoubtedly focused attention on the staphylococcus as a major cause of infections which have become difficult to treat satisfactorily with antibiotics This is in sharp contrast to the continued success of antibiotics in the treatment of many other serious infections

Data from several sources indicate that staphylococcic infections actually are increasing in frequency and severity During the past 3 4 year an unusual number of outbreaks has been reported from nurseries for the newborn manifested as pyodermas pneumonia empyema osteomyelitis septicemia and diarrhea Infection of surgical wounds with staphylococcus has also gained prominence with increasing numbers of infections of so called clean wound Staphylococci have also become the most important secondary invaders in patients with debilitating disease and in unconscious patients

Hospitals in which the problem has been intensively studied report an increasing number of cases of pneumonia bacteremia and endocarditis caused by the staphylococcus and an increasing mortality from such infections despite intensive antibacterial therapy Although the major interest in antibiotic resistant staphylococci has been focused in hospitals the same difficulties may exist on a community wide basis

In retrospect there is little evidence that the early sulfonamides were of any great benefit in serious staphylococcic infections Resistance to them has been demonstrated in the course of treatment and most strains of pathogenic staphylococci are now partially or totally resistant to these drug

Penicillin was the first important antibiotic and still is the leading one in many respects The increasing incidence of resistant strains associated with production of penicillinase by the organism and the increasing incidence of hypersensitivity reactions by patients treated with penicillin have reduced its effectiveness

Streptomycin may occasionally be helpful as an adjunctive agent in the treatment of staphylococcic infect Bacit

cin one of the polypeptide antibiotics is active in vitro against most pathogenic strains There is no cross resistance between bacitracin and any of the other useful antibiotics and it is of most value when used topically either alone or combined with other agents in infected serous cavities the cerebrospinal canal and on surface infections Occasionally results are satisfactory when it is used alone but its major value in serious systemic infections is in combination with other antibiotics

The tetracyclines are broad spectrum antibiotics with considerable activity against staphylococci Their action is chiefly bacteriostatic although in high concentrations they are also bactericidal Antibacterial activity is similar for all three congeners—chlortetracycline oxytetracycline and tet racycline There is almost complete cross resistance among them but chlortetracycline has appreciably greater anti staphylococcic activity weight for weight than either of the others Unfortunately the widespread use of this group of antibiotics especially in hospitals has resulted in the emer gence of large numbers of resistant strains of staphylococci

The antistaphylococcic activity of chloramphenicol is ap preciably less than that of the tetracyclines Resistance de velops slowly in vitro Chloramphenicol used alone is some times effective but its major value is in combination with other more effective agents particularly erythromycin or novobiocin

Erythromycin is the most active antistaphylococcic agent next to penicillin However resistance to it develops readily in vitro and also in vivo during therapy Many reports indi cate successful use of erythromycin alone in serious staphy lococcic infections but it gives best results when combined with other antibiotics

The growing problems involved in the control of the staphylococcus have led to concentrated efforts to discover new more effective antibiotics of which several seem to be promising

Carbomycin has an identical spectrum of activity with erythromycin but usually is less active For this reason it has not been recommended as a useful antistaphylococcic antibiotic

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confused because of its early use in combination with other antibiotics particularly penicillin and tetracycline When used alone studies indicate that this drug is effective against various infections caused by organisms within its spectrum of in vitro activity It is impossible to judge its relative effectiveness compared with erythromycin which is so much more active in vitro The eventual place of oleandomycin in therapy still is unknown Certainly any fixed combination of oleandomycin with tetracycline or other drugs cannot be recommended Each is to be used for its own activity in the doses required to produce such activity

Other antistaphylococcic antibiotics unrelated to the erythromycin group have recently become available These are novobiocin vancomycin ristocetin and kanamycin

Novobiocin (Albamycin* Cathomycin Cardelmycin Valcamycina also formerly called Streptonivicin and Cathocin) is of clinical value against infections with susceptible organisms and is particularly useful combined with other effective agents in treating staphylococcic infections that have resisted therapy with many other current antibiotics Three important factor limit its usefulness the high degree of binding to serum protein which probably limits its in vivo activity the rapid rate at which organisms particularly staphylococci become resistant to it and the occurrence of rashes fever and other sensitization phenomena These are more common when the daily dose exceeds 2 Gm

Vancomycin is predominantly bactericidal active chiefly against gram positive bacteria particularly staphylococci It can be used for systemic infections only if given intravenously Effective blood levels can be maintained for almost 12 hours by injection of 500 mg or a single dose of 1 Gm daily Clinical data are still sparse but results have been encouraging in some infections resistant to other antibiotics

Ristocetin (Spontin*) is somewhat less active than vancomycin It must be given intravenously for systemic infections in daily doses of 2-4 Gm or more in 2-4 injections

Kanamycin (Kantrex) a new Japanese antibiotic is related to neomycin chemically and in its antimicrobial action Cross resistance has been observed in vitro It is not absorbed to any significant extent from the gastrointestinal tract but intramuscular injections appear to be well tolerated In doses of 1 3 Gm daily granular casts appear with

significant albuminuria or hematuria pyuria or nitrogen retention The possibility of more serious renal toxicity and auditory nerve damage on occasions must be considered Satisfactory clinical effects have been observed in some cases of serious staphylococcic infections and in infections of the urinary tract

► [This is a good short statement of the present situation in the most perplexing problem in antimicrobial therapy —Ed.]

URINARY TRACT INFECTIONS

Screening Method for Evaluation of Urinary Tract Infections in Female Patients without Catheterization Early accurate diagnosis and adequate therapy are important in the management of urinary tract infections In the later stages chronic pyelonephritis uremia or hypertension may develop Minor symptoms or minimal pyuria is often the only clinical finding even in serious infection Bacteriologic evaluation of patients with seemingly insignificant symptoms is thus important if it can be done without hazard The common technic in females involves use of bladder catheterization but this carries the hazard of introducing organisms which can produce urinary tract infection Such a risk must be weighed against the possibility of overlooking relatively silent infections

Quantitative bacterial counts help in the evaluation of catheterized urine specimens Over 10 000 bacterial colonies/ml urine are usually found with infection whereas contaminants rarely exceed concentrations of 1 000 colonies/ml urine Burtis R Boshell and Jay P Sanford[6] (Harvard Med School) believe that this method if reliable can be applied to the study of clean voided urine specimens from the female and should offer a safe method of screening patients with minor symptoms suggestive of infection

TECHNIC —A clean voided specimen was obtained by having the patient sit in a Sitz chair previously filled with green soap solution and wash the labia perineum and inguinal region carefully for about 5 minutes The urethral orifice and surrounding areas were scrubbed with Zephiran* sponges The patient then moved to a commode or stool chair and was instructed to hold the labia apart and void The first portion of the sample was discarded and the rest was collected in

(6) A I t Med 48 1040 1045 May 1958

two sterile tubes one of which was examined routinely and the other cultured All specimens were cultured within 60 minutes of collection Another group of patients was instructed to stop voiding as soon as the clean voided specimen was obtained Each patient was catheterized immediately and the specimen cultured Clean voided specimens from the first group of patients containing over 1 600 colonies/ml urine were also cultured

The authors conclude that quantitative bacterial counts are necessary to evaluate any urine culture and that a properly collected clean voided specimen is adequate for culture in both males and females The major advantage of this collection technic is that it allows accurate diagnosis without catheterization and the risk of bladder infection

► [With increasing acceptance of the notion that catheterization of the urinary bladder entails a risk of infection several groups have attempted to devise methods of obtaining satisfactory urine specimens from female patients without catheterization These first 2 articles indicate that practical methods of obtaining reasonably clean mid stream specimens are available —Ed]

Evaluation of Method for Detecting and Following Urinary Tract Infection in Females without Catheterization Traditionally to evaluate urinary tract infections in females urine has been obtained by catheter and voided specimens have been considered worthless because of contamination from the external genitalia However catheterization is dangerous because it may actually produce infection by introducing the bacteria into the urinary tract

Harris D Riley Jr [7] (Vanderbilt Univ) describes a method for obtaining satisfactory urine specimens by a voided technic even though the patients were extensively paralyzed after poliomyelitis

Method —With the patient in the dorsal lithotomy position the external genitalia are scrubbed thoroughly with soap followed by water and benzalkonium hydrochloride 1 1000 The patient is encouraged to void and the specimen is collected from the midportion of the urinary stream into a sterile container which is immediately transported to the laboratory The specimen is processed at once or stored in ice for no longer than 3 hours

In 42 patients the bacterial species isolated from voided specimens were compared with those from corresponding catheter specimens obtained on the same day The two methods correlated well The same bacterial species were usually isolated in paired specimens Cultures sterile by one procedure were most often sterile by the other When females without clinical evidence of urinary tract infection were cath

(7) J Lab & Clin Med 5 840 848 Dec 1958

eterized 26% had urine free from bacteria 40% had less than 100 bacteria/ml and 30% had less than 1 000 bacteria/ml Pathologic findings compatible with pyelonephritis are much more common in patients with bacterial counts of 100 000/ml or more than in those without significant bacteriuria Bacteriuria is significant when bacterial counts are 100 000/ml urine or more Values significantly lower than this usually represent contamination

Comparison of Bacterial Counts of Urine Obtained by Needle Aspiration of Bladder Catheterization and Midstream Voided Methods was made by Ofelia T Monzon Edwin M Ory Harold L Dobson Edward Carter and Ellard M Yow[8] (Houston) In the past few years much interest has been centered on the problem of distinguishing true bacteriuria from contamination of the urine specimens The urethra is known normally to harbor bacteria which may then contaminate specimens obtained by catheterization or by voiding

METHOD —Patients were instructed not to void and when the urinary bladder was sufficiently distended the suprapubic area was cleaned with antiseptic solution with the patient supine By use of a 20 ml syringe and 20 or 22 gauge spinal needle the urinary bladder was entered through the anterior abdominal wall in the midline 1 cm above the symphysis pubis after preliminary subcutaneous infiltration with 1% procaine solution Immediately after adequate urine was withdrawn for study midstream voided and catheterized specimens were collected All specimens were immediately cultured in broth and by agar pour plate technic incubated and read 48 hours later

Of the 34 study patients all but 9 had diabetes Twenty seven had sterile cultures of the aspirated specimen though 4 of these showed positive cultures of the catheterized specimens Seven had positive cultures of all specimens Of this group 5 had colony counts of over 100 000 organisms/ml urine Patients belonging to the group showing positive cultures of the catheterized specimens and those with sterile aspirated specimens had colony counts much below 100 000/ml urine Hemolytic Staphylococcus aureus was cultured from 3 specimens obtained by bladder aspiration from 6 by catheterization and from 13 midstream specimens

A greater number of sterile specimens was obtained by suprapubic aspiration of the urinary bladder There was good correlation between colony counts of 100 000 organisms/ml

(8) New England J Med 259 764-76 Oct 16 1958

urine and the presence of pyelonephritis There was no appreciable difference if the colony counts of specimens obtained by any of the three procedures were above 100 000 bacteria/ml urine The significance of colony counts below this number is less clear *Results suggest that low colony counts in the urine are primarily caused by urethral contamination*

► [This worthwhile study bears out the contention that passing a catheter through the urethra always entails risk of transferring small numbers of bacteria from the urethral canal into the bladder cavity That being the case the only dependable criterion of pre existing infection is the finding of many bacteria e g over 10 000 organisms/cc urine —Ed]

Urinary Tract Infection in Paralytic Poliomyelitis was studied by Harris D Riley Jr and Vernon Knight[9] Infection of the urinary tract is a common serious complication in paralytic poliomyelitis characterized by indolence chronicity few symptoms and persistent heavy bacteriuria The infection appears to depend on the combined effect of factors inherent in severe poliomyelitis and its treatment including immobilization urolithiasis catheterization of the urinary bladder and possibly on some effect of antibacterial treatment

During 21 months 44 such patients were seen at the Poliomyelitis Respiratory Center at Vanderbilt University Hospital Urine was collected for study without catheterization Comparisons of bacterial counts of urine obtained by the clean voided technic with urine obtained by catheter from the same patient showed excellent correlation between the two methods *Fifteen patients with severe infection had* bacteriuria of at least 10 colonies/ml urine Antimicrobial therapy was seldom effective Some patients showed recurrent symptoms of urinary infection whereas others despite persistent heavy bacteriuria were asymptomatic Of the 44 patients with urinary infection 28 had few or no symptoms referable to the urinary tract The symptomatology in 16 patients was characterized by frequency dysuria and fever Chills were rare as was flank pain Of 183 specimens with bacterial counts of 10^5/ml or more obtained from 20 patients only 54% showed pyuria

Bladder catheterization favored development of urinary tract infection Although age did not seem to be a determining factor females appeared predisposed to infection They

(9) M d 37 81 297 D mbe 1958

were catheterized oftener than males which undoubtedly contributed to the development of the infection Urinary calculi were demonstrated in 21 patients

In patients hospitalized in the acute stage of poliomyelitis the first positive cultures usually contained Escherichia coli When catheterization was used an enterococcus was often noted However in a relatively short time and usually after antimicrobial therapy the urinary flora in most patients changed to aerobacter proteus or pseudomonas species which are naturally resistant to antibiotic therapy or rapidly become so In most patients one of these species persisted

Urinary tract infection constitutes one of the most important aspects of paralytic poliomyelitis

Hospital Infection of Urinary Tract with Proteus Clinical Bacteriologic Study with Special Reference to Modes of Infection L I debo and G Laurell[1] (Uppsala) state that some decades ago proteus was so rarely isolated from infected patients that it was considered an almost harmless saprophyte The incidence is gradually increasing however particularly in urinary tract infections and even in a few septic conditions Urinary tract infection caused by proteus is now one of the infections most often acquired in hospitals

Within 1 year 125 such infections were recorded in an Uppsala hospital The proteus strains isolated showed a high resistance to antibiotic This factor and the similarity of resistance characteristics suggested a hospital infection Clinically these infections showed a predilection for older patients and those with serious basic diseases or functional disorders of the urinary tract It appeared that the administration of antibiotics favored the selection of certain resistant strains which were capable of spreading to the environment Indirect infection by contact with nursing utensils in daily use appeared to be a prime factor Bedpans cloth to cover the pans and rectal thermometers were particularly heavily contaminated Even clean rectal thermometers in some instances yielded hospital type proteus The heavy contamination of these thermometers (up to 70%) led to a rapid spread of proteus to the rectum of almost every patient an important factor in auto infection of the urinary tract with hospital strains

(1) Acta path et microb scand 43 93 105 1958

Response of Infected Urinary Tract to Bacterial Pyrogen Chronic pyelonephritis is difficult to diagnose M A Pears and B J Houghton (London) describe a new, simple method to diagnose renal infection Bacterial products are given parenterally and the urine examined for kidney sensitivity The excretion rate of white and nonsquamous epithelial cells increases

METHOD —The rate of urinary cellular excretion was determined in three specimens of urine collected hourly before intravenous injection of 0 007 µg/g body weight of Pyrexal a purified lipopolysaccharide derived from Salmonella abortus equi Four specimens were collected at 30 minute intervals starting from the time of collection of the last control specimen The cellular excretion rate of white and nonsquamous epithelial cells was determined in each of the seven specimens

The difference between means of the cellular excretion rate in the three preinjection periods and the first two post injection periods were calculated The mean differences in 10 patients in whom the diagnosis of chronic renal infection was established was an increase of 186% In contrast 6 normal controls had a mean decrease of 10% The probability of obtaining such a result fortuitously is less than 1 in 100 but more than 1 in 1 000 No correlation was noted between urine flow and cellular excretion rate

In all patients the rise in cellular excretion occurred within 30 minutes a considerable time before onset of rigor or fever In some the excretion rate fell as the temperature rose The phenomenon may be a hypersensitivity of a site of infection to parenterally administered heterologous bacterial products with obvious resemblance to that described by Sanarelli and Shwartzman

► [This interesting observation strongly suggests that bacterial endotoxins exert some influence on the inflammatory response to localized infection by gram negative bacilli As a diagnostic test the procedure seems too tedious to come into wide use —Ed]

BACTERIAL ENDOCARDITIS

Diagnostic Aspects of Subacute Bacterial Endocarditis in the Elderly In several series of reported cases 10-50% of the patients with subacute bacterial endocarditis were over age 50 The disease usually occurs in persons with diseased

(2) Lancet 2 128 129 July 19 1958

hearts Because more such people for various reasons are living to old age a greater frequency of subacute bacterial endocarditis in the elderly can be expected in the future In this age group it is often atypical and easily overlooked

W J Gleckler[3] (San Mateo Calif) reports his findings in 10 patients 6 men and 4 women aged 57 81 seen consecutively during the past decade Three showed typical clinical features with heart murmur fever leukocytosis splenomegaly anemia weight loss and emboli Seven were difficult diagnostic problems and diagnosis was made in only 3 of these

CASE 1 —Man 81 confused delirious with paranoid ideas progressive weakness occasional slight temperature elevations and systolic apical murmur died in coma

CASE 2 —Woman 68 was thought to have senile delirium or a mild senile psychosis She had heart murmur fever and sterile blood cultures Autopsy showed multiple cerebral emboli due to subacute bacterial endocarditis

CASE 3 —Man 67 had classic involutional melancholia that cleared after the subacute bacterial endocarditis was adequately treated

Psychoses may be the presenting symptom of subacute bacterial endocarditis as illustrated in these 3 patients

CASE 4 —Man 68 had signs symptoms and laboratory findings of liver disease that disappeared after the subacute bacterial endocarditis was treated

CASE 5 —Man 69 had progressive uremia that clinically appeared to be due to resistant Escherichia coli pyelonephritis Autopsy revealed subacute bacterial endocarditis with diffuse glomerulitis

CASE 6 —Man 64 who was observed daily for 6 weeks had normal temperature but complained of anorexia and weight loss Examination revealed a heart murmur Blood cultures proved subacute bacterial endocarditis that cleared with treatment

CASE 7 —Woman 60 had hypertension She sustained a cerebral hemorrhage and died in coma Autopsy showed that the cause of the cerebral lesion was subacute bacterial endocarditis rather than hypertensive cardiovascular disease

The presence of a murmur noted on physical examination in each of these patients is helpful in making the correct diagnosis

Splinter Hemorrhages are recognized as a characteristic physical sign in patients with subacute bacterial endocarditis Margaret M Platts and Mavis S Greaves[4] (Sheffield Univ) examined the fingernail of 429 patients and normal persons and those of 35 cadavers The lesions classed as splinter hemorrhages usually brown or black were all beneath

(3) A M A A h I t Med 10 761 65 N mbe 1959
(4) Bri M J 143 144 J l 19 1959

the fingernails When fresh they were red but changed color within a few days They did not blanch on pressure The hemorrhages were 1 3 mm long linear and longitudinally situated beneath the distal third of the nail They did not fade or disappear spontaneously but grew out with the nails and eventually could be cut off

Splinter hemorrhages were found in 77 of the persons examined 60 had more than one lesion The highest incidence (86%) was in 7 persons who had recent major arterial emboli 5 had mitral stenosis 1 had partially treated bacterial endocarditis and 1 recent coronary thrombosis Capillary fragility was no greater among patients with splinter hemorrhages

Nail parings containing splinter hemorrhages that had grown out were treated with benzidine and barium peroxide and gave the green coloration characteristic of altered blood The lesions consisted of a homogeneous mass of altered blood embedded in a layer of squamous cells adherent to the undersurface of the cut nail Their frequency in patients with uninfected mitral stenosis and with no signs of active rheumatic disease makes it unlikely that they are due to a toxic process acting on the capillaries The high incidence in these persons and those who had recent large emboli supports the other clinical evidence which suggests that the lesions are embolic

► [It is helpful to learn how often splinter hemorrhages can be found in diseases other than bacterial endocarditis The most remarkable examples of these lesions I have seen were in patients with severe trichinosis There the distal nail beds may be bordered by dozens of these lesions —Ed]

TOXOPLASMOSIS

Glandular Toxoplasmosis Survey of 30 Cases Not all toxoplasma infection can be congenital nor are the manifestations of acquired infection always severe J K A Beverley and C P Beattie[5] (Univ of Sheffield) direct attention to the glandular form of toxoplasmosis which appears to be the commonest manifestation of acquired infection Thirty cases are reviewed

Isolation of the parasite by animal inoculation is the most

(5) Lancet 2 379 384 Aug 23 1958

reliable method of diagnosis Since this is not always possible or successful diagnosis must often rest on serologic tests For this study the authors chose an arbitrary level of a dye test titer of 1 256 and a complement fixation titer of 1 10

The case records revealed no characteristic clinical features Various diagnoses had been considered by the attending physicians in each case the most common being infectious mononucleosis others were tonsillitis Hodgkin's disease mumps lymphosarcoma leukemia aleukemic leukemia and poliomyelitis The signs and symptoms resemble those of infectious mononucleosis but none of the patients serums gave a positive Paul Bunnell reaction The first abnormality noted by 20 of the 30 patients or their parents was swelling or pain in the lymph nodes usually in the neck Any group of nodes may be affected and enlargement may be unilateral or bilateral It was a long time sometimes many months before the nodes returned to normal size

Headache was noted by 1 patient 3 had pains in the joints and limbs and 3 had abdominal pain Fatigue was common The spleen was enlarged in 5 patients 2 of whom also had hepatomegaly The blood picture showed an absolute leukocytosis in 6 patients and 5 others had leukocyte counts between 9 000 and 10 000 Lymphocytosis (under 5 years greater than 6 000 over 5 years greater than 3 000) was found in 15 patients Only 1 patient had pulmonary symptoms None had a rash and in none did any serious sequelae develop

Until more is known it must be assumed that human infection may come from various birds and mammals including man

► [It is difficult to avoid the conclusion that this must be a common clinical entity everywhere seldom recognized because facilities for doing the serologic tests are not generally available —Ed]

Glandular Toxoplasmosis Report on 23 Histologically Diagnosed Cases is presented by Erkki Saxen Lauri Saxen and Paul Gronroos[6] (Univ of Helsinki) Among 1 500 lymph node biopsy specimens glandular toxoplasmosis was found in 23 The specimens came from 22 women and 1 man over half were aged 18 35 Mean age was 32 After histologic studies serologic tests were done that confirmed the histologic impression in 82% In no patient was toxoplasmic disease suspected clinically

Besides follicular hyperplasia and sinus catarrh the lymph

(6) Acta path et microbiol scandinav 44 319 328 1958

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Nail parings containing splinter hemorrhages that had grown out were treated with benzidine and barium peroxide and gave the green coloration characteristic of altered blood The lesions consisted of a homogeneous mass of altered blood embedded in a layer of squamous cells adherent to the undersurface of the cut nail Their frequency in patients with uninfected mitral stenosis and with no signs of active rheumatic disease makes it unlikely that they are due to a toxic process acting on the capillaries The high incidence in these persons and those who had recent large emboli supports the other clinical evidence which suggests that the lesions are embolic

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exposure in lead mines in an area with a high prevalence of this disease Nodular lesions were found in the lungs but a tuberculin skin test was negative Bronchial secretions contained a large number of cryptococci Studies showed bilateral renal calcinosis azotemia and myriads of cryptococci in the urine A rapidly progressive picture of meningitis developed with deepening coma and the patient died after 5 days of treatment with amphotericin B orally

CASE 2—Woman 31 had chronic torula meningitis for 7 months before when amphotericin B was begun intravenously No portal of entry for the fungus or extracerebral focus of the disease was demonstrated After 1 month of therapy the headache cleared After 3 months the cerebrospinal fluid became normal and remained so Follow up 9 months later showed no recurrence and the patient returned to work as a medical secretary

CASE 3—Man 45 had a chronic central nervous system infection presumably cryptococcosis for 11 years During this time active pulmonary tuberculosis also developed but became inactive after treatment Cerebrospinal fluid was positive for Cryptococcus neoformans for 8 years Amphotericin B restored the cerebrospinal fluid to a more near normal pattern and sterilized it for fungi The residual neurologic abnormalities have not been altered which would indicate probable meningeal fibrosis and permanent neural damage

Amphotericin B must be adequately diluted in water (1 mg/10 ml) and administered by slow intravenous drip over several hours If the infusion rate is increased a pyrogenic reaction will result with local chemical thrombophlebitis Total daily dosage should be increased slowly to 1 mg/kg body weight In treating a chronic and diffuse granulomatous meningeal infection prolonged parenteral therapy would be necessary to insure adequate cerebrospinal fluid penetration by the drug

► [Although this form of meningitis is notorious for chronicity and long delayed relapses results reported in this and the following article make it seem that a real curative treatment is at last available—Ed]

Promising Results in Cryptococcic Meningitis Long considered a rare and fatal infection cryptococcic meningitis is being reported with increasing frequency which may represent a true increase in incidence or merely greater awareness by the practitioner Fungous infections are more prominent in the differential diagnosis of infectious diseases probably related to the increased use of broad spectrum antibiotics steroids and cytotoxic drugs

Harry Rubin and Michael L Furcolow[8] (Univ of Kansas) report their experiences in treating 10 patients who had cryptococcic meningitis with amphotericin B (table) The drug was given intravenously 50 100 mg daily about 1

(8) N[illegible]logy 8 590 595 A[illegible]g 1 1958

nodes showed many enlarged epithelioid like cells solitary or in small groups that were sometimes situated in Flemming's centers but mostly in the medullary portion Large mononuclear cells with a hyperchromatic irregular nucleus indistinct borders and no observable nuclear structure were also encountered Another characteristic feature in the histologic picture was the abundant occurrence of histiocytes and mitoses in Flemming's centers The histiocytes contained much nuclear debris No necrosis giant cells or fibrosis were detected

On physical examination enlarged lymph nodes were observed in these sites 17 in the front of the neck 4 in the back of the neck 2 in the supraclavicular fossae and 2 in the groins The commonest site was under the ears along the border of the sternocleidomastoid muscle The glands varied in size from that of a bean to a hen's egg which was exceptional however Half of the patients stated that the glands were tender The blood picture examined in almost all patients was within normal limits Follow up studies in some patients for over 3 years showed all were asymptomatic

The clinical picture was characterized by the unspecificity and scantiness of symptoms which is also reflected by the fact that the doctors who had sent in the biopsy specimens had not suspected toxoplasmosis in any patient It is difficult to point to any clinical feature that would suggest the possibility of toxoplasmosis and constitute an indication for the performance of serologic tests It should however be noted that the glands were mostly hard and discrete thus differing from the glands in ordinary lymphadenitis

In glandular toxoplasmosis the histologic picture is diagnostic in most patients

MYCOTIC INFECTIONS

Treatment of Cryptococcic Meningitis with Amphotericin B A New Fungicidal Agent Martin J FitzPatrick Harry Rubin and Charles M Poser[7] (Univ of Kansas) report results in 3 patients treated with this drug in the past 1½ years

CASE 1 —Man 56 had silicosis from several years underground

(7) A Int M d 49 49 59 A g st 1958

exposure in lead mines in an area with a high prevalence of this dis ease Nodular lesions were found in the lungs but a tuberculin skin test was negative Bronchial secretions contained a large number of cryptococci Studies showed bilateral renal calcinosis azotemia and myriads of cryptococci in the urine A rapidly progressive picture of meningitis developed with deepening coma and the patient died after 5 days of treatment with amphoteri in B orally

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(8) Ne 1 gy 8 590 595 Aug t 1958

PATIENTS WITH CRYPTOCOCCIC MENINGITIS TREATED WITH INTRAVENOUS AMPHOTERICIN B

			P e Treatment		Post T e tm nt			
C e	Age	S x	Cl nical Status	Du a tion	Cl ni l Status	L ngth of Follow-up	Sp nal Fluid Find ngs	Sp nal Fluid Cultu e
1	31	F	Po	7 months	N rmal a t vities	13 mo ths	rmal	0 (14)
2	37	M	Poo	3 mo ths	N rm l ct iti	13 m nths	Normal	0 (8)
3	62	M	Poo	5 y a	Rel pse	14 mo ths	Ab orm l	0 (9)
4	31	M	C t al	4 month	Impro d	10 months	Normal	0 (1-)
5	45	M	P apl gic	10 ar	Un ha ged	9 m ths	Improved	0 (11)
6	63	M	M rib d	1 m th	Exp ed	—	Ab rmal	+
7	51	M	M b d	11 m th	Exp ed	—	Ab orm l	— (Pos tive on s ction)
8	5-	M	F	4 m ths	Imp ov d	3 mo ths	Imp o ed	0 (7)
9	64	M	Poo	8 month	Mod ate mpro em nt	4 months	Abnormal	+ (R lapse)
10	60	M	Poo	10 mo ths	Asympto mat c	2 months	Improved	0 (6)

All had abno m l c eb p al fl d w th po t c ltu es f r C yptococcu n f m bef t atn t

mg /kg body weight dissolved in 1 L of 5% glucose in wa ter and given over a minimum of 6 hours daily or every other day Total dose was 1 4 3 7 Gm in the 8 patients who survived

The most promising finding was the consistent cultural

sterility of the cerebrospinal fluid in 7 of the 8 survivors in culture and after animal inoculation This objective finding lends confidence to the definite impression that treatment has prolonged life in the 8 survivors

Side reactions to the drug were troublesome but did not require cessation of treatment in any patient A rising blood urea nitrogen should be anticipated

The Walworth Wisconsin Epidemic of Histoplasmosis Outbreaks of acute histoplasmosis are being recognized with increasing frequency A recent article by Lehan and Furcolow summarizes reports of 38 epidemics in this country and 3 abroad Kenneth R Wilcox Jr Burton A Waisbren and John Martin[9] report an epidemic with some unusual features Various types of exposure to a single source of the organisms occurred over 3 months and 19 persons became ill

All were associated in some way with the construction of a new house on a vacant lot A ditch was dug and water and sewer lines laid and connected This involved work by 7 of the patients The foundation was excavated footings dug and forms for the foundation placed and poured The 5 men doing this work subsequently became ill as did also 4 carpenters who visited the site while repairing the house next door On the 40th day after the work was begun soil specimens obtained by a public health physician (who also became ill) were found to contain *Histoplasma capsulatum* spore After the house was erected 2 men laying a pipe in the basement became severely ill with histoplasmosis

No building had apparently existed on the lot before Neither fowl nor animals had been kept or housed there At the time of the outbreak there was no evidence of bird droppings on the lot or on the sidewalk

The incubation period ranged from 7 to 16 days with a mean of 11 3 days Onset of illness was acute with fever malaise weakness and headache in 12 patients Chills and sweating were common Cough although not prominent was present in 18 Most had a hacking cough for a few days with small amounts of sputum Physical findings were minimal with only a few scattered crepitant rales

X ray study showed diffuse parenchymal nodules in 8 diffuse miliary nodules in 2 and diffuse bilateral mottling in 1 The first impression in 2 cases was that of metastatic car

(9) A Int Med 49 398 418 August 1958

PATIENTS WITH CRYPTOCOCCIC MENINGITIS TREATED WITH INTRAVENOUS AMPHOTERICIN B

Case	Age	Sex	Pre-Treatment: Clinical Status	Pre-Treatment: Duration	Post-Treatment: Clinical Status	Post-Treatment: Length of Follow-up	Post-Treatment: Spinal Fluid Findings	Post-Treatment: Spinal Fluid Culture
1	31	F	Poor	7 months	Normal activities	13 months	Normal	0 (14)
2	37	M	Poor	3 months	Normal activities	13 months	Normal	0 (8)
3	6[illegible]	M	Poor	5 years	Relapse	14 months	Abnormal	0 (9)
4	31	M	Critical	4 month	Improved	10 months	Normal	0 (12)
5	45	M	Paraplegic	10 years	Unchanged	9 months	Improved	0 (11)
6	63	M	Moribund	1 month	Expired	—	Abnormal	+
7	51	M	Moribund	11 months	Expired	—	Abnormal	— (Postmortem section)
8	52	M	Fair	4 months	Improved	3 months	Improved	0 (7)
9	64	F	Poor	8 months	Moderate improvement	4 months	Abnormal	+ (Relapse)
10	60	M	Poor	10 months	Asymptomatic	2 months	Improved	0 (8)

All had abnormal cerebrospinal fluid with positive culture for Cryptococcus neoformans before treatment

mg/kg body weight dissolved in 1 L of 5% glucose in water and given over a minimum of 6 hours daily or every other day Total dose was 1437 Gm in the 8 patients who survived

The most promising finding was the consistent cultural

and several clinical illnesses in the family were acquired

The house was in poor repair with loose siding and cornices containing apertures sufficiently large for the entrance of bats A *large* colony of the common brown or house bat Eptesicus fuscus and several bushels of bat guano were found in the attic No pathogenic fungi were *isolated* from 16 bats which were captured and killed in the laboratory *Histoplasma capsulatum* was isolated from soil samples collected some distance from the house and from 11 of 13 samples taken adjacent to the foundation

This study is especially significant as it may explain the prevalence of *histoplasmin* sensitivity and the occurrence of clinical cases of histoplasmosis *in* certain urban areas where the sources of infection are not yet recognized

This remarkable association of bats with a severe family epidemic of histoplasmosis and with the presence of histoplasma adjacent to the foundation of the house may not be unique *Bat feces* enrich the soil near a building infested by the house bat This is as *effective* in supporting growth of histoplasma as is bat guano in those caves associated with cases of histoplasmosis The wide distribution of the house bat and its *intimate* association with man and human dwellings may well support a widespread reservoir of histoplasma in soil to which man is often exposed

Vaginitis and Neonatal Infection Etiology of Mycosis in the Newborn was studied by J Bret Cl Coupe R Solle and H Marchand (Paris) in 300 *mothers* and their infants A smear was taken from the cul de sac and vaginal *walls of* 200 mothers at delivery and of 100 on admission Specimens were taken from the buccal cavity and nasal fossae of 200 infants at birth and 6 hours later and from the mouth nose stools and urine 24 hours and 4 days later These same studies were made on the other 100 infants 10 25 days after birth

Candida albicans was present in the vagina of 59 (20%) women and in *the* buccal and nasal cavities of 49 infants (16 3%) at birth all from mothers with positive cultures Thus 83% of women with vaginal moniliasis *transmitted* the infection to their infants during labor Smears of 40% of infants with mycosis at birth were still positive on the 10th day Besides the infants with mycotic infections at birth another 27 were contaminated in the hospital

(2) P m 4 66 937 938 My 4 1958

cinoma in 1 miliary tuberculosis and in another congestive failure Follow up x rays 1 year later showed no calcification These findings emphasize that the x ray appearance of the chest during the acute phase of disease is not pathognomonic for histoplasmosis If the diagnosis is suspected on other grounds the x ray may strongly support it

The leukocyte count of 8 patients varied from 6 600 to 18 300 with differential counts of 60 75% polymorphonuclears The histoplasmin skin test was positive in the 18 who were tested

A skin test survey was undertaken in the community and 112 persons gave positive reactions of whom 33 had complement fixation titers of 1 8 or over Within a block of the site of excavation 40% of persons had positive skin tests Evidently the site had been a source of recent acute infections which were either undiagnosed or not apparent The economic loss to the workers and to the owner of the lot was substantial Protection of persons subsequently using this site is a problem which has no clear cut answer

Acute epidemic histoplasmosis has a favorable prognosis After 1 year each person was back at work without complaint Long term follow up with pulmonary function studies will be necessary to rule out the possibility of future deterioration

Association of Bats with Histoplasmosis The saprophytic growth of histoplasma is so often associated with chicken excreta that it receives the immediate attention of the epidemiologist confronted by a case of histoplasmosis Any episode involving removal of litter and excreta from a chicken house or its use as a fertilizer is assumed to have provided effective exposure However many sites not associated with chickens have provided evidence of histoplasma

Chester W Emmons[1] (USPHS) suspected a relationship between this disease and the house bat when several members of a family became ill with histoplasmosis shortly after moving into an old frame dwelling in a rural neighborhood in Maryland The number of bats living in the attic of the house the quantity of bat guano found there and on the ground adjacent to the foundation walls and the isolation of histoplasma repeatedly from all sides of the house to a distance of 5 ft suggested the source from which one fatal

(1) P b H lth R p 73 590 595 J ly 1958

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( ) P méd 66 937 938 M y 24 1958

Spontaneous disappearance of infection in the newborn remains unexplained

Prophylaxis of neonatal infections consists of thorough bacteriologic investigation and treatment of vaginitis in the pregnant woman Determination of the organism responsible for the infection should always include bacteriologic study of vaginal secretions from the mother especially when detection is difficult in the infant as in hepatitis or pneumopathy

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BRUCELLOSIS

Brucellosis—*I Laboratory acquired acute infection* was studied by Robert W Trever Leighton E Cluff Richard N Peeler and Ivan L Bennett Jr[3] (Johns Hopkins Univ) in 60 patients These were among personnel of a bacteriology laboratory engaged in studies of *Brucella melitensis* and *Br suis* Follow up was carried out regularly by clinical examination and serologic tests before onset of the acute illness and for 1 or more years afterward Study of these patients made possible appraisal of the incubation period diagnostic procedures clinical manifestations efficacy of chemotherapy and development of chronic persistent symptoms (chronic brucellosis) The incubation period extended over a period of 2 8 weeks

With the exception of fever definite findings were few Splenomegaly occurred in 10% of the patients and hepatomegaly in 13% Jaundice was not observed In 46 patients one or more positive blood cultures was obtained during the acute illness In only 2 were no agglutinins detectable at time of onset of symptoms

Intradermal testing with Brucellergen® (suspension of nucleoprotein from brucella cells) or Brucellin® was carried out in 56 of the 60 patients before onset The initial skin test was positive in 3 Thirteen with negative skin tests before becoming ill were tested again at intervals varying from the day of onset to 14 months after recovery from acute brucellosis and in all the reaction had become positive

None of the drugs used produced a definite effect on the

(3) A M A Arch Int Med 103 381 39 March 1959

duration of fever recurrence of acute illness or development of chronic symptoms Streptomycin and tetracycline in combination were more successful than sulfadiazine in abolishing bacteremia during the treatment period but were not effective in preventing recurrence of bacteremia

Of the 60 patients 22 had recurrence of acute illness associated with bacteremia in 15 and with secondary elevation of the agglutinin titer in all In general symptoms and physical findings associated with recurrences were the same as seen during the initial illness though recurrent episodes were often milder The interval between seeming recovery from acute brucellosis and recurrence varied from 2 weeks to 11 months

The authors classified as having chronic brucellosis all patients with complaints of malaise fatigue myalgia arthralgia backache or feverishness for 1 year or longer beyond the acute illness unassociated with bacteremia changing serologic titer or physical abnormalities Of the 60 patients 24 were diagnosed as having chronic brucellosis

II Medical aspects of delayed convalescence are evaluated by Cluff Trever John B Imboden and Arthur Canter[4] Of 24 patients who had acute brucellosis due to infection with Br suis or Br melitensis 4 8 years previously in 16 symptoms of depression fatigue sexual impotence and vague aches and pains developed after the acute disease and diagnosis was chronic brucellosis The other 8 recovered completely Clinical study did not demonstrate a difference between the two groups except for the continued symptoms of poor health

Spink has listed three possible explanations for the complaints associated with chronic disability after brucellosis (1) continued active brucella infection (2) possibly psychoneurotic or neurasthenic patients and (3) possible organic brain damage as a result of the acute brucellosis producing the nonspecific symptoms of ill health

In the present study there was no evidence of persistent infection with brucella in the patients Prolonged elevation of agglutinin titer above 1 100 in some patients and persistence of hypersensitivity to Prucellergin* might be indicative of continued presence of brucella in the tissues These findings however were no different in patients who recov

(4) A M A A h I t Med 103 398 40 M rch 1959

ered completely from those in patients who remained in ill health after the acute infection

Although several persons showed minor EEG abnormalities this was found as frequently in the recovered as in the chronically ill patients Organic brain damage detected by this means was not a feature of chronic brucellosis

Incidence of chronic brucellosis among the 60 patients from whom this follow up study was possible (40%) was considerably higher than incidence in other series An explanation for this is not readily apparent It is possible that the close surveillance of the patients arising from the nature of their occupation in laboratories dealing with infectious agents enabled and perhaps encouraged recognition of the symptoms that otherwise would not have come to the physician s attention In addition chronic brucellosis is a widely recognized though variably diagnosed entity and in these proved cases of acute brucellosis it is probable that vague symptoms of ill health after the acute infection were commonly interpreted as such

III Psychologic aspects of delayed convalescence were investigated by Imboden Canter Cluff and Trever [5] Brucellosis is usually a self limited disease Complications such as suppurative or granulomatous lesions may however occur In addition some patients remain disabled after the acute infection because of persistent symptoms in the absence of any demonstrable physical abnormalities and are commonly said to have chronic brucellosis Chronic brucellosis is clinically similar to neurosis in that nonspecific symptoms such as fatigue headache myalgia arthralgia nervousness and depression occur in absence of abnormal physical findings

Twenty four patients with a history of acute brucellosis 4 8 years previously were given a battery of psychologic tests and psychiatric interviews In 16 a chronic subjective syndrome developed after the acute illness 10 were still symptomatic 5 years later on the average Tenacity of the symptoms was impressive In 3 of the 6 chronic recovered patients symptoms were alleviated more or less concurrently with resolution of certain personal difficulties in their lives Recovery in 8 patients was uneventful

Psychologic testing of certain specific areas of intellectual functioning did not reveal evidence of organic brain dam

(5) A M A Arch Int Med 103 406 414 March 1959

age in the chronic or acute recovered groups Independent evaluation of the study patients by psychologic testing and psychiatric interviews did reveal evidence of emotional disturbance especially depression in the chronically ill patients Analysis of the data supports the view that the emotional disturbance is not merely secondary to the stress of illness but is more critically related to the pre illness personality structure and concurrent life situation

Factors that favor protraction of the chronic syndrome after it is established include the maintenance of self esteem afforded by somatic symptoms as an alternative to recognition of psychologic difficulty and the notorious reputation of brucellosis as a chronic disability

It is suggested that emotional disturbance constitutes the essential component of the chronic brucellosis syndrome

► [A valuable and unique study —Ed]

UNCOMMON COMPLICATIONS OF WELL KNOWN VIRUS DISEASES

Varicella Gangrenosa Albert M Crocker and J Neal Middelkamp[8] (St Louis) report a case

Boy 3 had varicella for 4 days before hospitalization because of left inguinal hernia One day before admission the father noticed a mass in the child s left inguinal region Examination showed crusting lesions of varicella on the face body and extremities The left scrotum was markedly tender with swelling and redness A mass was present that was not reducible and did not transilluminate light The impression was an incarcerated left inguinal hernia and varicella Surgical opinion was that a left inguinal herniorrhaphy should be done immediately At operation no hernial sac or hydrocele was demonstrated but the cord was greatly thickened and dark blue On palpation the pampiniform plexus was nodular and hard It was felt that this represented thrombosis of the pampiniform plexus The testis appeared viable and was placed back in the scrotum The immediate postoperative period was uneventful

On the 4th postoperative day (8 days after onset of varicella) bleeding occurred from the operative site and the nose and mouth Areas of ecchymoses were noted on the left thigh left calf distal third of the left leg and the lateral aspect of the right thigh Shock developed Hemoglobin was 4 2 Gm /100 ml and red blood cell count 1 630 000 White blood cells numbered 58 000 with a differential count of myelocytes 9 juveniles 14 stabs 21 segmentals 45 lymphocytes

(8) J Pediat 54 104 108 January 1959

11 Platelet count was 156 480 One unit of whole blood was given

On the 5th postoperative day examination of the lower extremities revealed small bullous lesions on the areas of ecchymoses The left foot was cool to palpation and bluish discoloration was noted on the dorsal and plantar surfaces of the left foot The areas of ecchymoses progressed from blue to black The toes became gangrenous and all sensation was lost Repeat blood studies revealed hemoglobin 6 Gm red blood cell count of 2 260 000 and platelet count of 162 400

The patient's hospital course was satisfactory with eventual sloughing of the superficial areas and amputation of the toes One month after hospitalization the patient received split thickness grafts to the previously gangrenous areas of the legs and thighs

It has been stated that gangrene is a rare complication of varicella and that it is seen in weak and malnourished children such as those who have tuberculosis Others have suspected that the gangrene is due to secondary infection by Staphylococcus aureus or hemolytic streptococci Still others have blamed vascular changes However gangrene has not been observed in every patient with varicella and purpura

Chickenpox Pneumonia Treated with Prednisolone Case Report is presented by C A Thompson and F P Cantrell[7] (Texarkana Tex) Severe widespread pneumonitis is a rare complication of varicella

Woman 31 had lesions on the face trunk and extremities 10 days after her children had chickenpox The lesions spread to involve the entire body A productive cough developed temperature rose to 103 104 F daily On the 4th day of illness he was admitted with large amounts of blood tinged sputum and dyspnea She was seriously ill respiration was labored at 36/minute she was cyanotic and coughed frequently raising large amounts of thin frothy pink tinged sputum The skin showed characteristic lesion of chickenpox Chest x ray showed widespread bilateral nodular pulmonary infiltrates Initial therapy included oxygen sedation and tetracycline Temperature remained between 101 and 104 F The sputum became more copious and frankly bloody and respirations remained labored and rapid Prednisolone in divided doses of 40 mg daily was given every 6 hours Within 24 hours the temperature was normal and the patient was less dyspneic and generally greatly improved

Pneumonitis is a serious complication of varicella In 51 cases reported in the literature there were 8 (16%) fatalities Steroid therapy in the present patient was begun only after considerable hesitancy and circumspection because she did not respond to supportive therapy within 72 hours and because of the high mortality in reported cases Further therapeutic trials with steroids seem warranted in certain viral diseases

(7) A n I t Med 49 1 39 1246 N mbe 1958

Thrombopenic Purpura as Complication of Mumps was observed by Charles P Kolars and Wesley W Spink[8] (Univ of Minnesota) in 2 women aged 27 and 65 and in 1 man 44 In the older woman the number of platelets remained low through the period of steroid therapy and splenectomy was followed by only a transient rise in the platelet level In the younger woman steroid therapy did not abolish the thrombopenia but was helpful in controlling the bleeding tendency Again splenectomy failed to achieve any sustained rise in the platelet count The other patient had two acute complications of mumps orchitis and thrombopenia The hemorrhagic tendency was serious but persistent steroid therapy controlled the bleeding Although splenectomy was not done in this patient the natural course of the thrombopenic state was similar in character to that in the other 2 patients

Mumps is not an uncommon infection of adult life The complications can be painful and serious they include orchitis and meningoencephalitis Less commonly pancreatitis and oophoritis occur Thrombopenia which is potentially serious is a further complication The pathogenesis of these complications is not clearly understood Although direct invasion of the tissues by virus may be responsible for the inflammatory reaction the possibility also exists that a state of acquired hypersensitivity may be the cause

There is now substantial evidence that the inflammatory complications of orchitis and meningoencephalitis can be controlled by therapy with adrenocorticosteroids The authors observations indicate that steroid therapy is also effective in thrombopenia occurring as a complication of mumps

In reviewing the literature the authors were unable to find any documented instance of this complication occurring with mumps Perhaps thrombopenic purpura appears oftener in mumps than is realized since the 3 patients were seen over a relatively brief period

Thrombopenic and nonthrombopenic purpura are occasionally observed in patients with infectious diseases Clement and Diamond have reported on the findings in 96 children with thrombopenic purpura In 65 of these the purpura was associated mostly with upper respiratory infections but

(8) J A M A 168 2 13 15 Dec 27 1958

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(7) Am J Med 49 1239 1240 November 1958

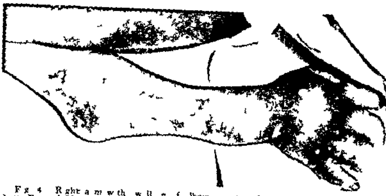
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F g 6 (ght) – Sam c se 3 th) te Fl)) t lack g p phy w h ex at f be ul t la fa
((C rt y f Cock b t P d Mac(g r M Q t J Med 7 36 7 387 J ly 1938)

usually the first symptom Once swelling had developed local tenderness and pain on movement were observed The underlying bones felt thickened and irregular They were never tender Low fever and minor leukocytosis were present

Among the 15 cases the radius was affected 28 time the ulna 26 the humerus 19 the metatarsals 7 the fibula and os calcis 7 the tibia and talus 5 and the metacarpals 3 times Early x rays showed only soft tissue swelling around the joint perhaps with indirect evidence of a joint effusion Later a band of osteoporosis appeared in the perimetaphy

it occurred also as a complication of rubella chickenpox (varicella) and infectious mononucleosis

Osteomyelitis Variolosa During an epidemic of smallpox in southwest Nigeria in 1957 Peter Cockshott and Malcolm MacGregor[9] (Univ College Hosp Ibadan) observed 15 children with a skeletal complication usually presenting as arthritis of the elbows This experience and a review of the literature led to the conclusion that bone and joint complications of smallpox are of two types (1) ordinary pyogenic



F g 4 R ght a m w th w ll g f lbow w t a d fing s (Cou tesy of Cock h tt P d M G g M Qu rt J M d 27 369 387 July 1959)

osteomyelitis which may occur in any acute infection though none occurred among the 15 cases and (2) osteomyelitis variolosa

Osteomyelitis variolosa affects children almost exclusively the majority being under age 5 though infants are not exempt Roughly this complication affects 0 25-0 5% of patients in a smallpox epidemic whereas it is liable to develop in 2 5% of affected children

The clinical types of osteomyelitis variolosa are bone disease alone or arthritis affecting one or more joints This complication occurs as readily after mild as after severe smallpox The precise time of onset is difficult to establish but in nearly all cases there is a latent interval of 1 6 weeks between onset of smallpox and appearance of joint symptoms The joints are frequently symmetrically involved with the elbows the commonest site (Fig 4)

As a rule the first sign was swelling around a joint Slight pain may be present initially but difficulty in movement was

(9) Q rt J M d 27 369 387 J ly 19 8

Of the 47 who had rubella during pregnancy in 8 the disease occurred during the 2d trimester and in 1 in the 3d All 9 had healthy children In 38 women the rubella was contracted during the 1st trimester Seven of these pregnancies ended in abortion 3 spontaneous 2 induced and 2 missed abortions the products of conception being passed later To the 31 women who went to term 25 healthy and 6 abnormal babies were born

Most people are aware that abnormal embryos are usually aborted spontaneously in the 1st trimester The prospective parents want to know therefore what the risk is of the birth of an abnormal fetus if the woman goes to term In the authors series the incidence of defective children born to mothers who carried to term after having had rubella in the 1st trimester was 19% or 1 in 5 Of the 6 abnormal infants 1 was stillborn and macerated and examination revealed a patent foramen ovale a patent ductus arteriosus and aspiration of meconium 1 had cataracts of both eyes congenital heart disease and thrombocytopenic purpura and died 3 weeks post partum 1 died at age 3 weeks with congenital heart disease 1 weighed 4 lb 15 oz at birth and survived but it has congenital cataracts and heart disease 1 was born with microphthalmus but is otherwise well and in 1 a heart murmur was noticed at 6 weeks of age but it is alive and well

Of 10 women given gamma globulin 2 contracted rubella in the 2d trimester Of the 8 who had rubella in the 1st trimester 1 aborted 1 had a live baby with heart disease and 1 had a macerated stillborn baby

Rubella Demonstration of Neutralizing Antibody in Gamma Globulin and Re Evaluation of Rubella Problem Results of the efficacy of gamma globulin for prevention of rubella have been equivocal Saul Krugman and Robert Ward (New York Univ) therefore tested for the presence of neutralizing antibody in ordinary gamma globulin convalescent phase rubella plasma gamma globulin prepared from the plasma of patients convalescent from rubella and normal human serum

These materials were mixed with thawed rubella virus and inoculated into comparable groups of 6 presumably susceptible children The dosage was 1 ml intramuscularly and

(4) New England J Med 259 16 19 Jl 3 1958

al region sharply demarcated on the epiphysial side but less well defined on the diaphysial aspect of the metaphysis (Fig 5) A thin shell of periosteal new bone was next seen to extend along one or more of the articulating bones and to invest the shafts It became incorporated with the shaft within 3 months by molding and left some thickening of the diaphysis especially near the capsular attachment where bilateral spurs were frequent The joint line was excavated in most instances (Fig 6) The lesion uniquely associated with this disorder is detachment or sequestration of the epiphysis apparently the result of the transverse metaphysitis

Chloramphenicol penicillin streptomycin chlortetracycline and oxytetracycline had no apparent effect The lesions tend toward recovery without treatment in a few months Eventual function is better than might be expected Serious sequelae depend on epiphysial damage or detachment and comprise reduction cessation or aberration of longitudinal bone growth with consequent shortening or limb distortion

Virus lesions of bone do occur Several cases of osteomyelitis in lymphogranuloma venereum and after prophylactic vaccination against smallpox have been reported Proved bone lesions of vaccinia virus resemble those of osteomyelitis variolosa

Invasion of the metaphysis is postulated as the pathogenesis of osteomyelitis variolosa In the stage of active growth in early childhood the metaphysis is especially vulnerable and the epiphysial center of ossification may become detached or destroyed Why the elbow joints are predominantly affected is unknown and no satisfactory hypothesis is yet available

RUBELLA

Rubella and Pregnancy Study of 47 Cases is presented by Harry Oxorn[1] (Montreal) An epidemic of rubella began in 1955 in Montreal A committee of the Montreal Obstetrical and Gynaecological Society studied the women who had rubella during pregnancy Most of the study patients were delivered in 1956 having had rubella in the latter half of 1955 or early part of 1956

(1) Am J Obst & Gyn 77 : 628-631 March 1959

The specific cause of the common cold is unknown In many instances the common cold has returned to haunt those who have reported isolation of the causative agent Since the beginning of the era of bacteriology at least seven bacteria have been considered definitive causes pneumococcus streptococcus influenza bacillus Micrococcus catarrhalis Bacillus septus M tetragenus and Friedlander s bacillus

A report of the transmission of the common cold to volunteers by filtered bacteria free nasal secretions led to doubt regarding the bacterial causation of colds Such transmission was confirmed by some investigators and denied by others

Many procedures and agents have been used for treatment and prevention of colds including various bacterial vaccines bacteriophage chlorine iodides quinine other drugs and various antiseptic substances None has been generally accepted or has proved effective in controlled studies Possibly one of the most unique methods devised was complete extirpation of the uvula a procedure termed staphylectomy which was claimed to reduce susceptibility to colds and catarrhal conditions after operation It is interesting that carefully controlled experiments have shown that any oral or parenteral placebo given for prevention of the common cold will apparently reduce the incidence as much as 50% compared with an untreated control group This may be the basis for the apparently beneficial effect of therapeutic and preventive measures used in the past

Epidemiologic studies have substantiated previous estimates of the occurrence on an average of 3-6 colds/person/year Attack rates have been shown to be higher in children and to decrease with age though immunity is apparently not a factor in this decrease Seasonal occurrence in the temperate zone has been substantiated but no relation to temperature change diet or other nonspecific factors has been established Reported studies suggest that chilling and exposure will not induce colds or increase susceptibility to experimental colds However curious features remain unexplained Despite the general concept that colds are infectious their transmission from an infected person to a group of apparently normal volunteers exposed under intimate circumstances has proved difficult Colds induced by inoculation

each dose contained an equal volume of virus and serum The results are shown in the table

Passive protection against rubella apparently can best be achieved by early administration of large doses of gamma globulin The exact dosage has not yet been determined In the meantime 0 15 0 20 ml /lb body weight appears to be indicated To women exposed during pregnancy 20 ml intramuscularly is suggested and all pregnant women in the 1st

DEMONSTRATION OF RUBELLA NEUTRALIZING ANTIBODY IN GAMMA GLOBULIN AND CONVALESCENT PHASE PLASMA

MATERIAL ADMINISTERED	NO OF SUBJECTS	NO CONTRACTING RUBELLA	INCUBATION PERIOD
			days
Rubella serum + normal serum (antibody)	6	5	15 15 15 17 17
Rubella serum + gamma globulin	6	1	17
Rubella serum + convalescent phase plasma	6	1	14
Rubella serum + convalescent phase gamma globulin	6	0	

Equal volume of rubella serum and material to be tested mixed and administered in dose of 1 ml intramuscularly

trimester with no previous history of rubella should be given the same dosage as soon after exposure as possible

► [*In the preceding study administration of gamma globulin did not seem helpful however the dose may have been inadequate or the injection may have been given too late When this kind of problem arises my inclination is to give the patient the benefit of a trial of gamma globulin* —Ed]

THE COMMON COLD

The Curious Case of the Common Cold John H Dingle[3] (Cleveland) considers the facts and concepts of the common cold and reviews some of the advances in knowledge in the past 20 years This infection is the most frequent ailment of mankind Despite considerable knowledge about it the disease remains elusive It is difficult to define sharply and clearly Its epidemiology is poorly understood and its causes —definitive predisposing and precipitating—are uncertain

(3) J Imm 1 81 91 97 July 1958

Washings from induced colds reproduce the disease whether filtered or not This clearly indicates a multiplying filtrable agent with the properties of a virus It survived well at –76 C and had a diameter as determined by filtration of 60 mμ or less Attempts at cultivation in fertile eggs or at transmission to animals were unsuccessful

Colds have not been produced by chilling or similar methods nor have these factors increased the susceptibility to a small dose of virus The prevalent belief that chilling causes colds possibly confuses cause and effect a feeling of chill on exposure to a draught may be the first symptom of a cold and not its cause A recent report indicates that chilling can precipitate a cold only in women at a particular phase of the menstrual cycle

Attempts to grow the cold virus in cultures of human tissues produced one line of virus which was propagated in cultures of human embryonic lung It was carried in series for ten passages producing colds over a period of 3 months in 13 of 92 volunteers (14%) the later passes doing as well as the earlier No cytopathic effects were detected in the cultures These results have not been duplicated and later culture material produced infrequent takes only in very early passages It is not known why the virus apparently grew for a while and was then lost

Possibly there is no single common cold virus The causes of colds may be many and various as indicated by recent evidence of diversity in virus properties

The JH virus seems to be associated with minor infections in children yet the infections were febrile in 23 of 26 children and not typical of colds Evidence that the JH virus causes colds in adults is equivocal

Some viruses multiply in tissue culture without evident cytopathic effects It appears possible that a virus may rapidly lose pathogenicity for man in culture—as influenza virus does on cultivation in eggs Perhaps the cold virus may lose pathogenicity on culture and at the same time visibly fail to damage the cultures hence cold viruses may actually be growing all the time without obvious evidence of doing so

Improved methods of isolation are revealing new respiratory viruses one after another and the outlook for increasing knowledge of this infection is hopeful Colds may prove to be caused by numerous viruses of equal importance or

and passed in successive groups of volunteers—so called pedigreed colds—rarely if ever spread secondarily

Factors of resistance and susceptibility remain puzzling but psychosomatic aspects may be important

Transmission studies using nasal secretions from persons with a cold have shown the virus to be stable in the frozen state but quickly inactivated by heat at 56 C Its size by filtration appears to be between 40 and 50 mμ The host range is limited to man and the chimpanzee

The problem of the cultivation of the agent of the common cold remains baffling The critical factors necessary for growth have not been defined and may or may not have been present in the experiments in which growth has been attempted The adenoviruses are not related to the ordinary common cold and in the noninstitutional civilian population they account for not more than 1 5% of respiratory infections

The available data indicate the lack of development of immunity and hence the probability that no specific vaccine will prove effective as a preventive measure even should it contain the true agent or agents of the common cold

► [In this section are articles by an American and an Englishman both of whom have directed long term studies on the common cold Despite devoted sustained effort aided by the best talent available they conclude that as of now the commonest disease of man remains a baffling mystery —Ed]

A Decade with the Common Cold C H Andrewes[4] (London) describes 10 years work at the Common Cold Research Unit at Salisbury in southern England The common cold is not amenable to study by simple laboratory technics so the presence of the virus has to be detected and studied in *human volunteers inoculated intranasally Over 5 000 volunteers* have been observed They were housed comfortably in pairs in single story buildings and remained isolated for 10 days They were allowed out for walks but had no other human contact After 4 days quarantine each received intranasal instillations of test material—washings from other colds control innocuous fluids or the results of attempted virus cultivation

Few of these experimental colds were febrile The most useful criterion of their presence was the amount of nasal secretion assessed by the numbers of paper handkerchiefs used daily

(4) B H J h H rk H p 103 1 7 J 1 1958

patients with bacterial pneumonia The temperature reached 101 F or higher in 90% All 5 patients with hemoptysis died Three had staphylococcic pneumonia and 2 an overwhelming pneumonia of uncertain cause Leukopenia was also an ominous prognostic sign 5 of 6 patients with white blood cell counts below 5 000 died

All patients with bacterial pneumonia received antibiotic therapy In pneumococcic infection penicillin was given in H influenzae infection streptomycin and chloramphenicol were given staphylococcic pneumonia was treated with massive doses of penicillin (20 000 000 100 000 000 units a day) streptomycin and erythromycin and/or chloramphenicol Antimicrobial therapy was promptly effective in 80% In several patients antibiotics were withheld for 48 72 hours and prompt improvement in clinical state and defervescence occurred after penicillin therapy was started

POLIOMYELITIS

Detecting Poliovirus in Vaccine Lots Used in Idaho in 1955 Carl M Eklund William J Hadlow Edgar G Pickens and Robert K Gerloff[6] studied in monkeys the two lots of the poliomyelitis vaccine that had caused paralytic poliomyelitis in Idaho children in 1955 The object was to detect virus and compare the relative susceptibility of children as determined by observations in the field and of monkeys as determined by laboratory experiences Inoculation of monkeys with the vaccine to determine its safety for man calls for a measure of comparison of the relative sensitivity of monkey and man to residual live virus in a vaccine

Inoculation of lots 6038 and 6039 into 32 000 children aged 6-8 resulted in paralytic poliomyelitis in 17 No extensive antibody surveys were made in Idaho before 1955 so the exact proportion of children susceptible to type 1 poliomyelitis is not known However in connection with the 1954 poliomyelitis vaccine evaluation study serums were obtained from children living in the more densely settled areas of Idaho and of these 50% had type 1 antibodies These data indicate paralytic attack rate of about 1 in 1 000 from 1 ml vaccine [illegible]culated intramuscularly

6 Pub Health Rep 74 60 f6 J 1959

these new viruses may be only on the periphery of the problem, with the common cold virus at the center Alternatively cold viruses may resemble the influenza A and perhaps ECHO and adenoviruses with a constant turnover one after another coming to dominate the scene

INFLUENZA

Pulmonary Infections Complicating Asian Influenza were studied by Robert G Petersdorf Joseph J Fusco Donald H Harter and Wilhelm S Albrink (New Haven Conn) in 91 hospitalized patients Eleven died 4 of whom were old and had been chronically ill Autopsy revealed hemorrhagic necrotizing pneumonia staphylococci and influenza virus were isolated from the lungs of 3 patients The uniformity of the clinical and pathologic picture in this group suggests that the virus is the primary etiologic agent in pneumonia associated with influenza These 11 patients represented the only fatalities in a community of 200 000 in which many thousands must have had the disease

The pulmonary complication was usually pneumonia developing especially in old men Women were most vulnerable during the childbearing period Ten of the 24 women in this age group were pregnant Bacterial pneumonia was observed in 38 patients Diplococcus pneumoniae was the cause in 24 patients hemolytic Staphylococcus (Micrococcus) pyogenes var aureus in 6 Hemophilus influenzae in 6 Proteus vulgaris in 1 and several species of bacteria in 1 The sputum of 43 patients in whom pulmonary infiltrates were demonstrated by x ray or at autopsy showed no predominant organism with gram stain and grew only normal mouth flora on culture

In about 50% of the patients an upper respiratory illness preceded the pneumonia There was sudden onset of headache malaise myalgia and chilly sensations about 1 week before hospitalization In the other patients symptoms of pulmonary involvement appeared concomitantly with headache muscle pain and fever Pleuritic pain occurred in one third of the patients Shaking chills were seen in 21 of 38

(5) A M A Arch Int Med 103 26 ?72 February 1959

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Inoculation of lots 6058 and 6039 into 32 000 children aged 6 8 resulted in paralytic poliomyelitis in 17 No extensive antibody surveys were made in Idaho before 1955 so the exact proportion of children susceptible to type 1 poliomyelitis is not known However in connection with the 1954 poliomyelitis vaccine evaluation study serums were obtained from children living in the more densely settled areas of Idaho and of these 50% had type 1 antibodies These data indicate a paralytic attack rate of about 1 in 1 000 from 1 ml vaccine inoculated intramuscularly

(6) Pub H lth R p 74 60 66 J a y 1959

A method of intraspinal inoculation which assured that the inoculum was actually placed in the spinal cord and vaccine inoculations directly into lymphoid tissue and brown fat proved to be a most sensitive test for detecting virus in monkeys Spinal cord blood lymphoid tissue and brown fat all had to be examined for virus Addition of Merthiolate* in concentration of 1 10 000 to the vaccine aided in isolation of type 1 poliovirus apparently by removing an interfering effect of type 2 virus

To attempt to get similar data regarding monkeys incidence of paralysis was recorded only on the basis of monkeys receiving successful intraspinal inoculation Although a total of 6 ml vaccine was given to each monkey only the 0 5 ml given intraspinally can be considered effective in producing paralysis With lot 6039 the paralytic rates approached 50% for all virus types With lot 6058 the rates were about one third that of lot 6039 but the results may have been influenced by the fact that lot 6058 was examined 6 8 months after studies of lot 6039 had been completed

With both lots of vaccine the incidence of paralysis was so much greater in monkeys than in children that a vaccine producing no paralysis in monkeys would be unlikely to have a deleterious effect on children

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DISEASES ASSOCIATED WITH NEWLY RECOGNIZED VIRUSES

Association of Hemadsorption Viruses with Respiratory Illness in Childhood Robert M Chanock Andrew Vargosko Alia Luckey M Katherine Cook Albert Z Kapikian Thomas Reichelderfer and Robert H Parrott[7] previously reported recovery of two new myxoviruses types 1 and 2 hemadsorption viruses from children with acute respiratory diseases such as croup pneumonia and severe pharyngitis In a study of 1 738 children in three Washington D C hospitals types 1 and 2 hemadsorption viruses were recovered almost exclusively from those with respiratory disease Results suggest that these agents play an etiologic role in respiratory illness The illnesses ranged from mild afebrile up

(7) J.A.M.A. 169 548 553 Feb 7 1959

per respiratory disease to the syndromes of pneumonia or croup

The virus recovery rate among patients with respiratory disease was 2 3% for type 1 and 3 9% for type 2 The amount of illness associated with these agents was higher (19 5%) when estimated by the complement fixation technic The highest rate of virus recovery (16 7%) or complement fixing antibody rise (30 2%) occurred for type 2 virus in patients with the croup syndrome

Dissemination of types 1 and 2 viruses during most of the fall winter and early spring of 1957 58 contrasted with the pattern observed in the same population for Asian influ enza A The latter agent had a peak prevalence during Octo ber followed by low activity during November January and February as evidenced by virus isolation and serologic studies In unpublished studies evidence of year round oc currence of the hemadsorption viruses was obtained Type 1 or 2 virus was isolated during June July and August 1958 thus supplementing recovery of virus from October 1957 through May 1958 The recovery rate for these viruses dur ing the June through August period was 2 3% for types 1 and 2

New ECHO Viruses and Their Role in Human Disease are evaluated by Dorothy M Horstmann[8] (Yale Univ) The ECHO (enteric cytopathogenic human orphan) viruses have often been isolated from human excreta their di cov ery actually being a by product of tissue culture tests for the presence of polioviruses in fecal samples They cause specific cytopathic changes in certain primate tissue culture cells but (with some exceptions) do not produce disease in any of the usual laboratory animals The pattern of infection in families is similar to that associated with Coxsackie and polioviruses

ECHO types 4 6 and 9 have been as ociated with major outbreaks of aseptic meningitis in Europe and in the United States The size of most ECHO viruses is about 30 mμ Monkey kidney cells have proved the most sensitive system for their growth Antigenic diversity is one of the outstand ing features of the ECHO group and forms the basis of their classification into 20 serologic types

There are no distinguishing clinical features which indi

(8) A M A A h I t M d 102 155 162 J l 1958

cate that in a given patient the infection is due to a member of the ECHO group rather than one of the other enteroviruses but certain characteristics are helpful in suggesting the possibility One is the presence of rash To date rash has been noted in infections with ECHO virus types 4 6 9 and 16 and there has been an associated enanthema with types 9 and 16 Aside from rash the illnesses associated with ECHO virus infections have not been significantly different from aseptic meningitis or mild nonspecific febrile illnesses associated with other enteroviruses Moderate fever severe headache and stiff neck and/or back have been the most prominent features in those with central nervous system involvement

Cerebrospinal fluid findings have been as with other forms of aseptic meningitis lymphocytes predominate and total counts are usually in the range of 100 300 Isolation of certain ECHO viruses from the cerebrospinal fluid has been relatively common The extent to which ECHO viruses are capable of producing central nervous system damage in man is not clear

Laboratory diagnosis of ECHO virus infection depends on the availability of a viral diagnostic laboratory equipped with monkey kidney cell tissue cultures and typing serums against the known ECHO types

Further Studies of Epidemic of Exanthem Associated with Aseptic Meningitis The pattern of disease is changing in that some diseases are diminishing in frequency and severity whereas others are increasing D A J Tyrrell K R Lane and B Snell[9] (Univ of Sheffield) describe their experiences with a syndrome apparently caused by a virus which became prevalent for the first time in 1956 in Western Europe and North America with extensive outbreaks in England Germany Belgium Canada and Iceland ECHO virus type 9 was readily isolated in many of these outbreaks

Differences in the clinical picture described by several observers may be partly due to differences in selection of cases (e g degree of severity in hospital cases) and also to diagnostic selection as a large proportion of patients seen were not tested for virus infection Only the general practitioner if he sees enough cases is in a position to recognize the full range of clinical manifestations However rashes may have

(9) Quart J Med 7 3 3 333 July 1958

been more prominent in some outbreaks than in others

The range of clinical patterns presented by the illness is illustrated by four main types short indeterminate illness (Ca e 1) rash (Case 2) rash and meningitis (Case 3) meningitis (Case 4) and a more severe disease complex (Ca e 5)

CASE 1 (12 cases) —Girl 10 awoke with a headache and malaise remained in bed 3 days and recovered completely in 1 week A throat swab on the 2d day yielded a virus During the illness virus neutralizing antibody titer rose from 16 to 256

CASE 2 (12 cases) —Boy aged 12 months became irritable and refused food The next day a few purplish red macules appeared on the



Fig 7 Fig 8 (Court y f Ty r ll D A J t l Qu rt. J M d 7 323 333 July 19 8)

fa e The rash rapidly became blotchy and spread by the 4th day over the face trunk and buttocks (Figs 7 and 8) No neck stiffness or mouth lesions appeared Slight rhinorrh a increased to a mucopuru l nt discharge The skin did not appear normal until 2 weeks after on set of illness and the child remained irritable for several weeks Virus was recovered from a throat swab and the feces on the 3d day of illness

CASE 3 (7 ca es) —Girl 3 had transient mild upper respiratory infection After about 10 days she complained of headache refused food vomited and had a temperature of 103 F The next day head ache was more severe there was abdominal and left groin pain and vomiting or retching occurred every 15 minutes A fine macular rash appeared on the face and the cheeks were flu hed Cervical lymph no les were enlarged and the neck and back were moderately stiff Virus was recovered from a throat swab Symptoms di appeared about 2 we ks after onset

CASE 4 (3 cases) —Girl 9 had thirst retrosternal pain and severe

frontal headache The next day headache was more intense and vomiting was frequent On the 3d day she was hospitalized with a low fever and slight stiffness of the neck and back Several small white spots were seen bilaterally on the buccal mucous membrane opposite the upper molar teeth Anterior cervical and inguinal lymph nodes were palpable Cerebrospinal fluid showed increased lymphocytes and protein Recovery was complete in 10 days

CASE 5 —Man 40 father of 5 children of whom 4 were ill with rash and headache had fluctuating severe headaches for 4 days with sleepiness sore throat and generalized aching Temperature was 101 F He was disoriented in time and his thoughts were sluggish Neck stiffness and Kernig s sign were present Cerebrospinal fluid showed increased lymphocytes and protein A faint blotchy erythema appeared over the upper trunk Numerous white dots and small pinless ulcers were present around the papillae of Stensen s ducts Virus antibody titer rose from 128 to 512 though nose and throat swabs yielded no virus Recovery was complete in 17 days

The illness was characterized by a maculopapular rash aseptic meningitis and lesions of the buccal mucous membrane The clinical picture varied—a fact realized only because family epidemics were studied as well as hospital patients No such epidemics have been known before the last few years However individual cases would not have been recognized as a specific infection in the absence of an epidemic The rashes might have been labeled rubella or atypical rubella or heat or food rash Lymphadenopathy fever and rash might suggest infectious mononucleosis and meningism alone might have been called aseptic meningitis or nonparalytic poliomyelitis

Study of Illness in Group of Cleveland Families XV Acquisition of Type Specific Adenovirus Antibodies in First Five Years of Life—Implications for Use of Adenovirus Vaccine Adenovirus antibodies are common in civilian populations yet a number of studies have shown consistently that these viruses cause only 0 5 3% of respiratory illnesses in families college students and adults Clinical adenovirus infections may be uncommon in the groups studied because immunity may have developed as a result of such infections earlier William S Jordan Jr George F Badger and John H Dingle[1] (Western Reserve Univ) measured the time and frequency of acquisition of type specific antibodies since birth by children in a group of Cleveland families

Findings showed that maternal adenovirus antibodies were freely transferred across the placenta but at age 6

(1) New England J Med 258 1041 1044 May 22 1958

months most children had no adenovirus antibody As meas ured by antibody acquisition types 1 and 2 infections were common during the first 5 years By age 5 the percentage of children with types 1 2 and 6 antibodies was the same as that in the adult group Infections due to types 3 5 and 7 were relatively infrequent the prevalence of the different antibodies at age 5 being about half the adult level

From these data and those of other studies the authors conclude that the generalized use of adenovirus vaccine in civilian populations is not warranted at present

Varied Clinical Manifestations of Coxsackie Virus Infec tions Observations and Comments on Outbreak in Cali fornia are presented by Robert B Gordon Edwin H Len nette and Rachel S Sandrock (Berkeley Calif) The known Cox ackie viruses have been separated into two groups on the basis of histopathologic changes produced in the mouse There are at least 19 immunologically different viruses in group A and 5 immunologically different types in group B Although the Coxsackie viruses have a ubiquitous distribu tion and can be found in the stools of normal persons their causal relation to certain diseases has been established

The outbreak of Coxsackie virus disease in California in 1956 was primarily manifested by pleurodynia but aseptic meningitis pericarditis and pleural effusion were also seen The infections were due principally to Coxsackie virus type B 5 This is believed to be the first time that this immuno logic type was incriminated in epidemic pleurodynia Well over 500 persons were affected in Shasta County and envi rons *alone during the late summer and fall of 1956 Of 60* study patients 30 were aged 0 19 and 47 0-29

The incubation period is about 2-4 days Onset is generally sudden and is often heralded by sudden severe thoracic pain usually at the level of the diaphragm and often without pro dromal signs Pain is severe and lancinating occurring uni laterally or bilaterally In some persons especially children the pain is abdominal tending toward the epigastrium and eliciting protective splinting of the abdominal musculature The temperature usually reaches 100 101 F and occasion ally 103 F and is accompanied by a rapid pulse Pain and fever usually last 1 2 days then subside Differential diagno sis has to con ider appendicitis pancreatitis common bile

( ) A M A A h I t M d 103 63 75 J u y 1959

duct obstruction acute cholecystitis perforated peptic ulcer coronary insufficiency pneumonia and pulmonary infarction

The authors encountered not only patients with a pure aseptic meningitis picture and those with an essentially pure pleurodyneal picture but also patients with a combination of both

No myocarditis was seen in infants Pericarditis associated with pleurodynia was observed in 7 males This suggests that the group B Coxsackie viruses are the probable etiologic agents in at least some patients with acute benign pericarditis

Acute Benign Pericarditis Report of Two Cases Associated with Group A and Group B Coxsackie Viruses Group A Coxsackie viruses of which there are at least 19 immunologically different virus types are known to cause herpangina and are strongly suspected of being a factor in meningo encephalitis Those of group B which contains 5 immunologically different types are now generally accepted as causing Bornholm disease and some conditions classified as aseptic meningitis More recently the Coxsackie viruses have been causally linked to several cases of acute myocarditis which otherwise would have been considered idiopathic

The association of idiopathic or acute benign pericarditis with diseases of known viral etiology just as in idiopathic myocarditis has led to the suspicion that at least some pericarditides may be of viral origin

Eli R Movitt Edwin H Lennette (Univ of California) Jack F Mangum Morris Berk and Murdock S Bowman[3] (V A Hosp Oakland Calif) report 2 cases of pericarditis associated with infection due to the Coxsackie virus These are the first reported cases in which the virus was recovered from the stools and a rise in humoral antibody levels to the recovered virus was demonstrated

Case 1—Man 26 had anterior chest pain Examination showed an increased area of cardiac dullness a pericardial friction rub temperature of 100 8 F and a white blood cell count of 20 800 A roentgenogram showed marked enlargement of the cardiac silhouette and an ECG revealed slight elevation of S T segments While in hospital the patient expectorated small amounts of dark red blood A pericardial tap produced 50 ml fluid which appeared almost like pure blood Pericardial biopsy showed no histologic changes compatible with a tuberculous process but an organizing hemorrhagic exudate was noted on one surface composed of masses of red cells fibrin proliferating fibroblasts and capillaries

(3) New England J Med 258 108 1086 May 29 1958

A suspension of the biopsy tissue was inoculated intracerebrally into adult mice and intraperitoneally and intracerebrally into 2 litters of 1 day old mice An aliquot was also inoculated into tissue culture tubes No agent was recovered in any of these host systems

Two stool specimens yielded a virus identified as Coxsackie virus group B type 3 The acute phase blood specimen gave a neutralization index of 1 8 log and the convalescent phase specimen 3 3 log indicating a 30 fold rise in antibody level This small but demonstrable rise in titer is significant since the virus to which an antibody response was elicited was recovered in the stool

CASE 2—Man 74 had chills fever substernal pain a faint pericardial friction rub and temperature of 101 F The white blood cell count was 9 450 and a roentgenogram showed a slightly enlarged cardiac silhouette On the 3d hospital day the rub increased in intensity A stool specimen yielded a virus subsequently identified as Coxsackie virus group A type 1 The acute phase blood specimen had a neutralizing capacity of 2 6 log the convalescent phase blood specimen 4 log Inability to detect more than this 25 fold rise in neutralizing capacity during the illness most likely is attributable to the high antibody level already present at the time the first blood specimen was drawn Despite it low magnitude the rise is significant since the same immunologic type virus was excreted in the stool

Although the Coxsackie viruses are ubiquitous and may be recovered from persons without objective or subjective evidence of illness there is ample evidence that they have an etiologic role in human disease Additional studies will be required however to indict definitively and unequivocally the Coxsackie viruses as incitants of acute benign pericarditis

Severe Generalized Disease (Encephalohepatomyocarditis) Occurring in Newborn Period and Due to Infection with Coxsackie Virus Group B Evidence of Intrauterine Infection with This Agent Infection with group B Coxsackie viruses during the neonatal period may cause severe and often fatal disease characterized primarily by myocarditis and/or meningoencephalitis Sidney Kibrick and Kurt Benirschke[4] (Harvard Med School) report 2 cases both fatal

CASE 1—Boy aged 2 days had feeding difficulties and vomiting On the 5th day rectal temperature was 38 9 C on the 7th day he had anorexia lethargy and fever and on the 10th day sudden cyanosis developed At this time he was in acute respiratory distress convulsing intermittently moribund had peripheral edema and rales at the lung bases The liver was palpable 7 cm below the costal margin The ECG showed nonspecific changes He died 4½ hours later At autopsy the lungs were severely congested the heart weighed 49 5 Gm (expected weight 19 Gm) Microscopically the myocardium showed widespread muscle necrobiosis and inflammation The liver was grossly congested and had large areas of central necrosis The

(4) P d t 2 857 875 N mbe 1958

meninges showed minimal increase in the number of inflammatory cells A transmissible cytopathogenic agent was isolated repeatedly from the myocardial tissue subsequently identified as Coxsackie virus group B type 4

CASE 2—Girl aged 13 hours had a rash and edema petechiae scleral hemorrhages and pitting edema Nine days ante partum the parents and 2 siblings had respiratory illness and 7 days ante partum the mother probably had pleurodynia At age 30 hours the patient hemorrhaged from the mouth Penicillin and streptomycin were started She had intermittent hematemesis and edema became more pronounced A convulsion occurred at age 35 hours and she died at age 36 hours At autopsy petechiae and edema were found The gastrointestinal hemorrhage was due to esophageal and gastric erosions and she had massive pulmonary hemorrhage The heart was slightly dilated Transmissible cytopathogenic agents were recovered in cultures of monkey renal cells from the myocardial liver and spinal cord tissue but not from the blood psoas muscle or lung These were identified as Coxsackie virus group B type 4

Story of Shipyard Eye is recounted by Ernest Jawetz[5] (Univ of California) In 1889 several Austrian ophthalmologists described a disease entity characterized by acute conjunctivitis with extreme edema of the conjunctiva pain photophobia and lacrimation followed by superficial erosions of the cornea and finally by deeper opaque subepithelial corneal infiltrates located just beneath Bowman s membrane These opacities were round located mainly in the center of the cornea and persisted for up to 2 years

During the summer of 1941 a large outbreak (over 10 000 cases) occurred in Hawaii at the naval shipyards of Pearl Harbor Soon thereafter the illness appeared on the west coast of the United States Several thousand cases were diagnosed most of which appeared in workers in shipyards Members of their families and other close contacts were rarely affected The disease has been called epidemic keratoconjunctivitis or shipyard eye

Scrapings were taken from the conjunctivas of a seaman who had had intensely painful red eyes for 12 days The illness had started on board ship several days after his departure from an oriental port with inflammation in the right eye and had spread to the left eye about 4 days later The scrapings were inoculated into tissue cultures of strain HeLa cells After an unusually protracted period of incubation these cultures yielded a cytopathogenic virus subsequently established as the prototype of adenovirus type 8 Some 100

(5) B M J 1 873 876 Ap 4 1959

strains of this agent have been isolated all over the world all from the eye and with rare exceptions all from typical cases of epidemic keratoconjunctivitis The etiologic role of adenovirus type 8 in this condition has been proved by inoculation of volunteers

The adult is not highly susceptible to adenovirus infection the eye being the sole portal of entry and the principal susceptible tissue Infection is likely to occur only if a large inoculum is placed directly into the eye The person most likely to accomplish such a transfer appears to be a nurse or physician engaged in examining the eye Thus epidemic keratoconjunctivitis in the western world appears to be largely an iatrogenic disease The shipyard with its chemical and mechanical irritants brings many workers to the dispensary where doctor or nurse may inoculate them with adenovirus type 8 while attempting to remove a foreign body

For oriental countries an alternative epidemiologic pattern may be proposed Small children appear to be relatively susceptible to adenovirus infection They might spread the agent effectively to other children (possibly through respiratory or gastrointestinal excretions) and to adults

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TOXINS AND ANTITOXINS

Neonatal Tetanus in Nigeria Between April 1953 and August 1956 A B Tompkins[6] (Univ College Ibadan) treated 141 newborn infants with tetanus The infection arises when the cord is cut at birth often with a sharp stick or palm leaf and is then dressed with various unsterile materials including clay salt shea butter a mixture of gin and palm oil and native medicine which may contain cow dung Finally a hot fomentation is applied

The incubation period averages 7 7 days The onset interval is the period which elapses between the appearance of the first symptom—usually failure to suck—and onset of tetanic spasms Case mortality has been found to vary inversely with duration of the onset interval which varies from a few hours to several days Usually the clinical course

(6) B r M J 1 138 1385 J 14 1958

is rapid and severe rigidity and frequent spasms develop in less than 24 hours

Simple dressings were applied to the umbilicus when necessary No other local treatment was used All patients received 150 000 300 000 units of procaine penicillin daily The dose of antitoxin ranged from 0 to 100 000 units given as a single intramuscular injection soon after admission Mortality did not differ significantly with different doses but it was concluded that 50 000 units of antitoxin is adequate in neonatal tetanus Intramuscular paraldehyde was given in doses of 0 5 1 ml as required Sodium phenobarbitone 65 mg on admission and repeated after 3 4 days acted as a basal sedative and was supplemented with intramuscular paraldehyde when necessary This combination was thought to give a smoother sedation than paraldehyde alone

Many babies apparently died of asphyxia caused by inhalation of regurgitated milk To avoid this danger those who were severely ill were not fed orally but hydration was maintained by daily subcutaneous infusions of 4 3% dextrose in 0 18% saline Tracheotomy was not used but it is possible that the lives of several patients might have been saved by it

The mortality rate was 89 6% including patients who died within 24 hours of admission

Discussion on Tetanus is presented by G Payling Wright D R Laurence E B Adams and A Crampton Smith[7] Wright points out that a second dose of antitoxin is eliminated much faster than the first After a patient has received an injection of any horse serum antitoxin irrespective of the disease for which it may have been given he should be promptly immunized against diphtheria and tetanus with the appropriate toxoid By thus creating the state of active immunity which can be effected without any unpleasant side effects future passive protection against these diseases with horse serum antitoxin is rendered unnecessary

Clinical trials in tetanus were set up by Adams and Laurence The aim was to compare two different treatment methods practiced concurrently while keeping all other factors constant Attempt was made to eliminate the influence of variables over which there is no control by taking sufficiently large samples and allocating patients randomly to their treatment group The most important of these variables

(7) Proc R Soc Med 51 997 1008 December 1958

is the severity of the disease as judged by the length of incubation occurrence of reflex spasms their frequency and severity and the period that elapses between the first symptom of tetanus and the first reflex spasm The patient s age wound site and standard of nursing care also affect the outcome of treatment By using sets of randomized envelopes patients were allocated without conscious selection to treatment groups in which the only difference was in the choice of drug to control reflex spasms In this way an attempt was made to assess the value of different methods of treatment in particular that of chlorpromazine

Compared with sedation methods previously used chlorpromazine did not reduce the mortality rate Previous claims for various successful treatment methods would not stand critical review because they were not derived from *properly conducted clinical trials*

Adams plans to evaluate the role of tracheotomy in treatment of severe tetanus All patients will be treated with a mixture of chlorpromazine and barbiturate whereas one group selected by the same method of random sampling will be subjected to tracheotomy Later use of muscle relaxants will be studied and positive pressure respiration by a similar technic

Smith believes that in a few patients spasms cannot be controlled except by paralysis with curare but the amount needed to control these spasms will paralyze all the patient s voluntary muscles This situation must be accepted and artificial respiration regarded as inevitable in patients with tetanus treated with curare

Importance of Intravenous Injection of Diphtheria Antiserum When diphtheria is suspected injection of antidiphtheritic *serum is indicated without delay but opinions differ* as to the best route A Tasman J E Minkenhof H H Vink A C Brandwijk and L Smith[8] investigated the excretion of antitoxin through the salivary glands after it had been injected intramuscularly and intravenously

The salivary excretion of antitoxin is important Of 13 patients tested by intravenous injection 12 had antitoxin in the saliva in 30 minutes and had therefore become atoxic (table) *The intravenously injected antitoxin immediately brings the patient s serum up to titer* whereas intramus

(8) La t 1 1299 1304 Ju 21 1958

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(7) Proc Roy Soc Med 51 997 1008 December 1958

since the beginning of the study Streptococcic infections have been detected by bacteriologic and immunologic tech nics Recurrences of rheumatic fever were diagnosed by the modified Jones criteria

The 3 year follow up showed the following incidence of streptococcic infections per patient year in each group sul fadiazine 21 1% penicillin by mouth 20 7% and penicillin by injection 7 3% When the group of patients taking the agents by mouth was divided into those who maintained good prophylaxis and those who did not it was found that the injections were still more effective than either prepara tion given orally for the prevention of streptococcic infec tions and that sulfadiazine was more effective than penicil lin by mouth if good prophylaxis was maintained The re currence rate of rheumatic fever per patient year was as fol lows sulfadiazine 1 9% penicillin tablets 5% and penicil lin injections 0 3%

► [A pretty convincing argument for the use of long acting penicillin given by injection —Ed]

New Approach to Treatment of Acute Rheumatic Fever is described by Samuel Vaisman Louis Rakita Edward A Mortimer Jr Julio Guasch Augusto Schuster Alberto Vig nau Richard B Roberts Richard M Krause and Charles H Rammelkamp Jr [1] Because the etiologic relation be tween acute rheumatic fever and group A streptococcus is well established it was attempted to determine the effect of eliminating these organisms in patients with acute rheu matic fever Penicillin was selected as the therapeutic agent because of its demonstrated effectiveness in eradicating streptococci and preventing acute rheumatic fever Large doses were used because it had been shown by several inde pendent investigators that group A streptococci could be cultured from the involved valves in patients dying dur ing an acute attack of rheumatic fever

Penicillin was given intramuscularly to 49 patients 3 000 000 units of sodium penicillin daily for 10 days 1 200 000 units of procaine penicillin daily from the 11th through the 21st day and 1 200 000 units of benzathine penicillin on the 22d day Besides penicillin acetylsalicylic acid was given Acetylsalicylic acid only was given to 48 controls There were no essential differences between the penicillin

(1) Tr A Am Phy 71 74 80 1958

EXCRETION OF ANTITOXIN IN SALIVA

Intramuscular injection (a erage dose 28 000 A.U)		Intravenous injection (average dose 12 000 A U)	
No of cases	Time taken for antitoxin to reach saliva	No of cases	Time taken for antitoxin to reach saliva
1	30 min.	12	30 min
3	4 5 hr	1	6 hr
3	10 hr		
9	1–9 days		

cularly injected antitoxin is slowly absorbed absorption usually not being complete for about 4 days sometimes 6

Experiments on guinea pigs indicate that intravenous injection of antiserum will result in fewer heart lesions (myocarditis and fatty degeneration) fewer postdiphtheritic paralyses and a lower mortality than intramuscular injection

RHEUMATIC FEVER

Controlled Study of Three Methods of Prophylaxis against Streptococcic Infection in Population of Rheumatic Children II Results of First Three Years of Study Including Methods for Evaluating Maintenance of Oral Prophylaxis are reported by Alvan K Feinstein Harrison F Wood Jeanne A Epstein Angelo Taranta Rita Simpson and Esther Tursky in collaboration with Thomas Argyros Julian Frieden Raymond C Haas Ilse Hirschfeld Arthur J Lewis Carlos Manso and Konrad Ulich[9]

In a special clinic designed to compare the effectiveness of three prophylaxis regimens in the prevention of streptococcic infections and rheumatic recurrences 391 children and adolescents with unequivocal previous attacks of rheumatic fever were studied At the start of the study a statistical method of random selection divided the patients into three groups comparable in age cardiac status and duration of freedom from rheumatic activity Each group was assigned to 1 of the 3 agents under study sulfadiazine 1 Gm /day by mouth potassium penicillin G 200 000 units/day by mouth and injections of benzathine penicillin G 1 200 000 units/month The patients have been examined monthly

(9) N w E gland J M d 260 697 0 Ap 2 1959

grating character of the pneumonia by x ray examination makes bacterial pneumonia unlikely

The changeable character of the x ray appearance of the lungs in the study patients would make it unlikely that the lung involvement was secondary to congestive failure to profound myocarditis or to pulmonary edema though the infiltrate on spot examination cannot be distinguished radiographically from acute pulmonary edema In microsections of the lungs from the patients who died it was easy to distinguish the pathologic picture of rheumatic pneumonitis from changes caused by congestive failure or pulmonary edema These three entities—congestive failure severe myocarditis and pulmonary edema—may be present concomitantly with the rheumatic pneumonitis and in the initial period of illness it may be impossible to distinguish them from rheumatic pneumonitis This however is not important because the initial therapeutic approach would not be essentially different even with associated rheumatic pneumonitis Later in the disease persistence of the x ray changes in the lungs should suggest the presence of rheumatic pneumonitis

The presence of rheumatic pneumonitis should certainly be considered a grave prognostic development in the course of rheumatic fever and a definite threat to survival In those who survive and whose pneumonitis clears there is severe residual heart disease Rheumatic pneumonitis calls for continued vigorous therapy until there is evidence of quiescence of the disease in the lungs as well as in the heart Hormone therapy should not be withheld

► [Some capable pathologists and clinicians deny the existence of rheumatic pneumonitis nevertheless there is much to support the concept Certainly it is true that the syndrome described here is not too rare and has serious prognostic implications —Ed]

ETIOLOGIC INFORMATION

Progressive Experimental Infection with Mycobacterium Leprae in Chimpanzee Preliminary Report Previous attempts to infect experimental animals with progressive leprosy by M leprae from human sources have been disappointing A E Gunders[3] (Harbel Liberia) inoculated a

(3) J Trop Med 61 28-30 September 1958

eated and control groups in the acute clinical course or lab atory findings though the rebound was somewhat greater the treated group

The final evaluation of the effect of therapy on valvular art disease was limited to 85 patients who did not show vious signs of previous rheumatic heart disease at onset of eatment Cardiac evaluation of these patients after 1 year a physician who was not aware of the type of therapy re aled organic murmurs in 19 penicillin treated patients d in 26 controls

The marked disparity in results during the acute and ronic phases of the illness suggests that the pathogenic echanisms involved in producing the acute phase phe omena and the chronic heart disease are not identical enicillin was effective in decreasing the incidence of heart sease but ineffective in controlling the acute phase mani stations Because the only known action of penicillin in ese circumstances is its antibacterial effect the data in cate that the continued presence of the streptococcus at me site in the body is important in the ultimate occurrence rheumatic valvular lesions and that elimination of these ganisms may be an important factor in determining nether rheumatic valvular disease will develop

[Before adopting a general policy of prolonged penicillin therapy for ite rheumatic fever one would like to see further work of this type —Ed]

Rheumatic Pneumonitis II Report on Clinical and Labo tory Findings in 23 Patients is presented by David Gold ig M Remsen Behrer George Brown and Gladden Elliott Vashington Univ) Sixteen died and autopsy revealed aracteristic but not specific microscopic changes in the ng parenchyma compatible with the diagnosis of rheu atic pneumonitis along with the usually observed changes rheumatic heart disease The 7 survivors showed clinical d laboratory findings strikingly similar to those of the 16 tients who died Though there has been some doubt about e existence and incidence of this rheumatic manifestation e authors feel that it does occur is not rare and can be dem strated by characteristic but not specific changes in the ng parenchyma

Rheumatic pneumonitis must be differentiated from bac rial or viral pneumonitis The zonal distribution and mi

(2) J P d t 33 547 565 Nov mbe 1958

nodules were located on the dorsum of both hands and feet most of them distal to the wrist and malleoli with the great est concentration on the lateral aspects An excised nodule showed a granulomatous process without typical giant cells Acid fast bacilli were found in all sections singly or in typi cal cigarette bunch formation By the end of the 14th month the nodules tended to regress

A second chimpanzee was inoculated with lepromatous material prepared in the same manner 1 ml injected sub arachnoidally and the rest subcutaneously and intrader mally into the right forearm No lesions developed in this animal Whether the route of inoculation or the age of the animal was responsible for success in the first animal i not known

Etiologic Agents of Varicella and Herpes Zoster Sero logic Studies with Viruses as Propagated in Vitro Investi gations on varicella and herpes zoster have been limited by lack of an overtly susceptible animal or a means to propa gate the viruses Procedures have now been developed for propagating these viruses in vitro

Thomas H Weller and Helen M Witton[4] (Harvard Univ) devised a complement fixation test using antigens prepared from infected cultures and an in vitro neutralization tech nic Human embryonic skin muscle tissue was used almost exclusively to prepare the cultures The viruses in vitro pro duce antigenic materials that can bind complement in the presence of convalescent phase serums from patients with varicella or herpes zoster Such serums specifically inhibit varicella and herpes zoster viral cytopathogenicity indicat ing that the etiologic agent is specifically present The rela tionship between zoster and varicella viruses was first sug gested in 1888 when in susceptible persons varicella was observed to develop after contact with patients who had her pes zoster Some experienced clinicians continue to question this hypothesis Immunologic studies using vesicle fluid as complement fixation antigen have shown the two entities to be closely related The accumulation of epidemiologic and laboratory evidence in support of the hypothesis of a single etiologic agent is impressive The burden of proof has now shifted to those who desire to refute the monistic concept

(4) J E pe Med 108 869 890 Dec 1 1958

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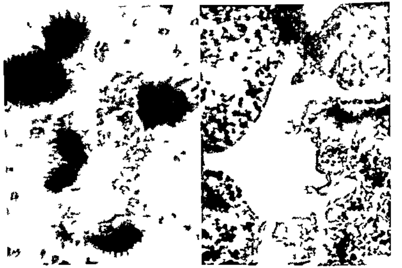
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Botryomycosis is characterized according to Donald J Winslow[5] (Armed Forces Inst of Pathology) by a chronic suppurative more or less granulomatous lesion containing specific fungous like grains or granules within suppurative foci These grains contain nonbranching bacteria that can be seen microscopically especially with Giemsa or Gram stains Human botryomycosis may be integumentary with or without muscular and skeletal involvement and visceral



Fg 10 (l ft) —Lung h wng m t oc b ll d adj c t to g l s G m ta d l f m ×1 500
Fg 11 (ght) —M n d m f foot h w g m ny oc w th g B wn d B n t n d d f m 1 500
(Courte y of W slow D J Am J P th 35 153 167 Ja F b 1959)

Integumentary distribution is more common with the hands feet and head the principal sites Six of 8 cases observed are described

CASE 1 —Man 60 died of refractory urinary infection An organism of the proteus group had been recovered repeatedly from the urine At autopsy the kidneys and lungs contained many abscesses from which a proteus micro organism was isolated Microscopically small gram negative coccobacilli were seen (Fig 10)

CASE 2 —Man 23 had a recurrent mass excised for the third time from the dorsum of the foot purulent material had been draining from it Microscopically the lesions consisted of focal granulomas with central suppuration Grains were found in many of the suppurative foci Gram stains revealed gram po itive cocci within the grains (Fig 11)

(5) Am J P th 35 153 167 J F b 1959

CASE 3—Man 38 had a rubbery lobulated mass arising in the distal palmar crease at the base of the right index finger Microscopically the granulomatous tissue revealed gram positive cocci but no fungi within the grains

CASE 4—Boy 8 had an infected foot At age 3 the foot was pierced by a piece of glass The puncture wound did not heal completely and multiple draining sinuses developed Original diagnosis was Madura foot Microscopically the Gram stain revealed many gram positive cocci within one of the grains

CASE 5—Man middle aged had a swollen submandibular lymph node The condition appeared compatible with actinomycosis A Gram stain revealed minute gram negative coccobacilli near the edge of some of the grains The review diagnosis was botryomycosis probably caused by a gram negative coccobacillus

CASE 6—Man 24 injured his right foot in 1945 Open reduction of a fracture was delayed until 1948 The foot became greatly swollen and indurated Multiple ulcers and open draining sinuses developed Madura foot was suspected Microscopic examination revealed typical botryomycotic grains within suppurative foci Special stains demonstrated cocci in the lesions but no fungi

In Cases 2 3 4 and 6 final diagnosis was botryomycosis probably caused by a staphylococcus

► [This is usually an indolent granulomatous chronically discharging lesion and may be confused with actinomycosis because the bacteria tend to clump into tiny granules The most frequent cause seems to be a gram positive coccus —Ed]

LUPUS ERYTHEMATOSUS

Lupoid Hepatitis and Hepatic Lesions of Systemic Lupus Erythematosus are discussed by Ian R Mackay L J Taft and D C Cowling[6] (Royal Melbourne Hosp) A positive lupus erythematosus cell test may be obtained in chronic hepatitis and cirrhosis representing lupoid hepatitis The lupus erythematosus phenomenon would indicate abnormal antibody formation in chronic hepatitis and may be responsible for the downward progress of the disease and also for certain other lupus manifestations which may supervene in lupoid hepatitis

The authors attempted to assess the relation of lupoid hepatitis to systemic lupus erythematosus by reviewing the clinical and pathologic features in 14 patients with lupoid hepatitis and analyzing the incidence and type of liver involvement in 19 patients with classic systemic lupus ery

(6) Lancet 1 65 69 J 10 1959

thematosus particularly by study of histologic material obtained at autopsy or by biopsy

Lupoid hepatitis occurs oftenest in young females The 14 study patients included 7 females and 4 males under 40 The hepatitis was unusually severe and progressive with recurrent exacerbations of jaundice and sometimes episodes of hepatic failure The biochemical tests of liver function were profoundly disturbed and the erythrocyte sedimentation rate was increased

Joint pains of the polyarthritic type were seen in 7 patients with objective evidence of joint disease in 2 Rashes were noted in 4 patients in 1 the rash persisted over the typical butterfly area of the face and responded to chloroquine Renal lesions developed in 3 Ulcerative colitis occurred in 3 Two patients had pleural effusion unassociated with pulmonary infection Hemolytic anemia with a positive Coombs test lymphadenopathy myocarditis and thrombocytopenia each occurred in 1 patient In 8 of the 14 patients only one positive L E cell test was obtained during the illness

Cortisone was given to 11 patients 4 received immediate and sustained benefit 1 had moderate remission 4 improved some and 2 derived no benefit As in other lupus manifestations the value of cortisone may be in controlling acute exacerbations of the disease it is uncertain whether long term maintenance therapy prevents or retards ultimate hepatic scarring

Of the 14 patients 8 died Liver failure occurred in 6 with an average course of 3 years At autopsy the liver was macroscopically and microscopically characteristic of active chronic hepatitis and presented obvious regenerative nodules and diffuse fibrosis resembling the appearance of postnecrotic cirrhosis Other histologic features were active necrosis in 6 cases and active parenchymal cell regeneration in 8

Lupoid hepatitis is distinguished from classic systemic lupus erythematosus because the liver disease is the initial and dominant lesion and determines the poor prognosis with death in liver failure other systemic manifestations if present are usually limited typical rashes are uncommon and anatomically the appearances in lupoid hepatitis are those of multinodular cirrhosis However varying degrees of systen involvement did occur in lup l hep

tients subsequently displayed such diffuse lesions that the ultimate diagnosis was debatable

Lupoid hepatitis and lupus erythematosus may be distinguished as separate entities by the clinical findings and pathologic changes but the occurrence of overlapping features in the two groups suggests a similar pathogenesis possibly mediated via abnormal immunologic responsiveness with autodestruction of host tissues

Pleuritis in Systemic Lupus Erythematosus Its Importance as Early Manifestation in Diagnosis Pleuritis with or without effusion is common in systemic lupus erythematosus Among 57 proved cases studied by William A Winslow Lester N Ploss and Bernard Loitman pleuritis was recorded in 41 In 7 of the others the patients had other pleural disease In 20 other patients whose x rays were not obtained pleuritis was noted in 10

Pleuritis is often an early sign In 3 patients it appeared as an isolated first sign in 16 others it appeared with few antecedent symptoms Despite its frequency as an early sign of systemic lupus erythematosus this disease is seldom considered in the differential diagnosis of idiopathic pleuritis The most striking antecedent symptom of systemic lupus erythematosus was arthritis or arthralgia Pneumonitis and pericarditis were also closely associated

The pleuritis in this series often cleared completely Of 39 patients followed by x ray in 14 one or more episodes cleared completely and in 8 all cleared except for minimal pleural residua Survival after the first pleuritic episode averaged 39 9 months with 23 of 42 patients still alive at last follow up Despite the tendency to frequent infections in systemic lupus erythematosus infectious neoplastic and metabolic causes of the pleuritis were ruled out in most cases

Unexplained pleuritis should be investigated for systemic lupus erythematosus as well as for tuberculosis or neoplasm

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RHEUMATIC DISORDERS

Course of Reiter s Syndrome When fully developed this syndrome is characterized by nonspecific urethritis arthritis and conjunctivitis George W Csonka[8] (London) ob

(7) A n. I t Med 49 0 88 J ly 1958
(8) Bri M J 1 1088-10 0 M y 10 1958

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was rarely mentioned as a conspicuous or dominant clinical finding in sarcoidosis However there is reason to believe that the joint disease is a manifestation of the sarcoidosis and that it occurs oftener than has been recognized in the past It has been confused at times with both rheumatic fever and rheumatoid arthritis

The authors *observed polyarthritis in* 5 young Negroes from the southeastern part of the United States Age at onset was 9 30 In 3 patients the arthritis was the initial or early manifestation of sarcoidosis in the other 2 it appeared about 2 years after other symptom The arthritis characteristically affected peripheral joints but in 1 patient the neck was also involved The joints were painful swollen and tender and sometimes also red and warm The discomfort was episodic and of short duration (3 28 days) in 2 patients but more protracted in the others In 4 there was no destruction of the joints but in 1 destruction was severe Fever was not a conspicuous feature except in the patient who lost 20 lb in a few weeks and who was the only one with appreciable leukocytosis

In each patient systems other than the joints were involved in the sarcoidosis Two had sarcoid of the skin 1 erythema nodosum 2 uveitis and other ocular lesions 4 pulmonary involvement and 4 had hilar adenopathy A degree of generalized superficial adenopathy was present in each

The diagnosis of sarcoidosis rested on the histologic demonstration of noncaseating miliary tubercles in various extra articular tissues in each patient the clinical syndrome involved in various combinations the lung lymph nodes skin and other systems hyperglobulinemia and failure of cultures of the lesions to yield growth of infectious organisms

Clinically the diagnosis of sarcoid arthritis should be suspected in acute recurrent or chronic polyarthritis associated with enlargement of the superficial or hilar lymph nodes Cutaneous ocular or pulmonary lesions when present make the diagnosis more likely

Sarcoid arthritis should be differentiated from rheumatoid arthritis and the polyarthritis of rheumatic fever

[This is a rarely mentioned manifestation of sarcoidosis —Ed.]

served 185 patients (182 men 3 women) with the syndrome during 1942 56 The small number of women confirms the general experience that they are rarely affected Of the 185 patients 87 had arthritis only and 98 showed additional features especially eye and skin involvement Most of the patients were sexually promiscuous Casual sexual relationship usually preceded onset of the genital infection leading to the syndrome Over 50% of the total had repeated attacks or continued activity over a number of years More than one attack of arthritis occurred in 104 patients and almost half of these claimed the later episodes were unprovoked because there had been no sexual intercourse during the preceding 2 3 months Urethritis was notably absent in some of these patients but there was an unusually high incidence of iritis and sacroiliitis In the whole series 21 patients had iritis occurring in 17 as probable relapses Of the 16 patients with sacroiliitis 9 were in this selected group

Reiter s syndrome was known to occur in only one family in which more than one member was affected These were 2 brothers who lived in different parts of England and who had severe attacks within 3 months of each other A common sexual source was denied

Many patients showed rapid evolution of the classic features of the syndrome in days or weeks but some showed marked dissociation in the interval between the appearance of cardinal symptoms One patient presented with nonspecific urethritis and 9 years later had a similar attack but with conjunctivitis for the first time Duration of first attacks in 165 patients ranged from 3 weeks to 18 months (mean 3 8 months) and in the other 20 the disease showed no clear cut remission from start to 3 or more years

No deaths were attributed to the syndrome The more important late changes were recurrent iritis in 21 foot deformities in 23 ankylosis of peripheral joints in 8 and sacroiliitis in 1 Of all the patients 28 had some permanent damage 6 others were handicapped with mild to moderate activity in various joints for 2 3 years but thus far no residual joint damage has been reported in any patient

Clinical and Pathologic Studies of Joint Involvement in Sarcoidosis were made by Leon Sokoloff and Joseph J Bunim[9] (Nat l Inst of Health) In past reports polyarthritis

(9) New E gl J Med 260 841 847 Ap 23 1959

time the serum is received to the completion of the test

Several thousand tests were performed in the authors lab oratory The stock bentonite suspension is stable for 6 months and the gamma globulin solution for 2 3 months Coated particles may be used satisfactorily after 3 weeks storage in the refrigerator Sufficient stock bentonite solu tion can be prepared at one time to perform 500 screening tests

Of 114 patients with verified rheumatoid arthritis the test finding was positive in 97 (85%) Disseminated lupus ery thematosus and scleroderma contributed the next highest percentage of positive tests 55 and 50%, respectively In 58 patients with nonrheumatoid arthritis the test was positive in 3 (5%) The test was positive in about 10% of syphilitic serums as well as in biologic false positive serums Positive results were obtained in 3 of 4 patients with Waldenstrom s macroglobulinemia In both tests human gamma globulin is used These results suggest that false positive results may be expected in serologic tests for rheumatoid arthritis in diseases in which macroglobulins are produced

Suppurative Arthritis Complicating Rheumatoid Arthri tis J H Kellgren J Ball R W Fairbrother and K L Barnes[2] (Univ of Manchester) observed 12 patients with rheumatoid arthritis in whom severe and sometimes fatal bacterial infection developed in connective tissue structures Nine had mainly suppurative arthritis often polyarticular in 2 the infection was mainly in the bones and 1 had mul tiple subcutaneous and muscular abscesses In 2 patients the infecting organism was coliform bacillus and in 10 staphy lococcus which in 7 patients was penicillin resistant

Because most patients had severe active rheumatoid arthri tis the increased swelling and pain in several joints and deterioration in general health was at first attributed to ex acerbation of the rheumatoid process In the early cases the correct diagnosis was made only after a swelling unex pectedly discharged pus or after multiple osteomyelitis or pyarthrosis was found at autopsy One major difficulty in correct diagnosis was lack of response to the infection e g 1 patient remained afebrile throughout with white cell counts of 4 300 and 5 800 though staphylococcic pus was present in three large joints

(2) B t M J 1 1193 1 00 M y 4 1958

Simple Rapid Diagnostic Test for Rheumatoid Arthritis —Bentonite Flocculation Test is described by Kurt J Bloch and Joseph J Bunim[1] (Nat l Inst of Health) An unusual serum protein that can react with gamma globulin is among the most constant laboratory findings in rheumatoid arthritis Demonstration of this rheumatoid factor by various

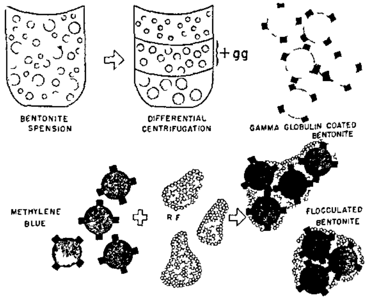


Fig 1 —Outl f b t t floc l t n te t B t t p t l p ted n wat d pt mum p t le bt n d by d ff t l t f g t n Part cl r o t d w th g mm gl b l n a d dy d w th methyl bl Rh m to d f t p ent p t t rum floc ul t t d p t cl (Cou t sy f Bloch K H d Bun m J J J A M A 169 307 314 J 24 1959)

serologic tests is one of the criteria for diagnosis of definite rheumatoid arthritis The rheumatoid factor is closely associated with the finding of subcutaneous nodules erosion of joint cartilage and destruction of subchondral bone Several laboratory procedures are available for demonstration of the rheumatoid factor The bentonite flocculation test (Fig 12) is a simple rapid sensitive procedure for detection of the rheumatoid factor Ingredients for the test are readily available from commercial sources and the necessary equipment is available in the average clinical laboratory Minimal technical skill is required for performance of the test and reading of results One hour or less is required from the

(1) J A M A 169 307 314 J 4 1959

damage to the animal s own intact thyroid gland Subse quently one lobe of a rabbit s thyroid gland was removed and thyroglobulin prepared from it was injected into the same animal s footpad Circulating antibodies were found in most animals tested after about 3 weeks When the remain ing lobe of the thyroid gland was removed a month later sections of the tissue were suggestive of those seen in Hashi moto s disease This surprising finding led to a search for thyroglobulin antibodies in patients with this disease Of 18 patients studied 12 had such antibodies

More recently investigators in Buenos Aires reported sig nificantly elevated values for serum gamma globulin in 4 pa tients with Hashimoto s disease

These observations prompted some British investigators to suggest that the serum abnormalities might represent an immunologic response They later found precipitins in the serum of 7 of 9 patients with Hashimoto s disease These antigen antibody precipitates formed when a layer of human thyroglobulin was placed over a layer of a patient s serum Precipitins to purified thyroglobulin also were demonstrated in the serum of 109 of 144 patients with Hashimoto s disease

The two lines of investigation have now converged The animal research succeeded in yielding autoantibodies to thy roglobulin and such antibodies were later found in pa tients with Hashimoto s disease Elevated gamma globulin in these patients suggested an immunologic abnormality which the finding of autoantibodies has confirmed How ever a third of the patients with Hashimoto s disease ex hibit no circulating precipitins or hemagglutinins

The serum of patients with Hashimoto s disease usually contains antibodies of the tanned cell agglutination type and of the complement fixing type This might suggest that these antibodies actually are one and the same but in other thy roid diseases particularly thyrotoxicosis only one or the other antibody is present

It is not known why the serum of patients with Hashi moto s disease regularly exhibits complement fixin anti bodies to an antigen obtained only from the gland of a thyro toxic patient Patients with Graves disease have this antibody frequently—45% in one series and 62 % in another —but its significance i unknown

The immunologic approach to Hashimoto disease has

In retrospect the most useful indication of bacterial infection was the occurrence of rigors The most useful investigation was aspiration of the more painful joints Aspiration and culture are indicated in every patient with rheumatoid arthritis who has suddenly deteriorated especially if there has been rigor Radiologic investigation is relatively unhelpful

Of the first 7 patients 5 died Prognosis can be improved if correct diagnosis is made early and the infecting organism cultured from the blood or infected joint for sensitivity tests Appropriate antibiotic therapy must be continued until the patient recovers Because bone infection is difficult to eradicate antibiotic therapy may have to be continued for many weeks Joints and bursae must be inspected daily for collections of pus because in patients with severe rheumatoid arthritis soft tissue abscesses or pyarthroses may develop with minimal local signs of inflammation Large collections of pus may be easily missed

Collections of pus may first be treated by aspiration and local instillation of appropriate antibiotic if not readily sterilized surgical drainage is indicated

► [It may indeed be difficult to recognize the existence of a suppurative arthritis in a patient with rheumatoid arthritis Such problems may become more frequent because of intra articular injection of steroids —Ed]

AUTOIMMUNE DISEASES

Review of Autoimmunization in Hashimoto s Disease According to Charles A Owen Jr[3] (Mayo Clinic) probably the most interesting development in the field of thyroid studies since the discovery of triiodothyronine is the finding of an antibody to thyroglobulin in the serum of certain patients with struma lymphomatosa (Hashimoto s disease) The discovery was the outcome of two independent lines of research one in America and one in Britain

The American investigators first obtained i o antibodies by sensitizing one rabbit to the thyroglobulin of another using improved technics of sensitization and measurement of the antibody titer Further considerations suggested that production of true autoantibodies should be accompanied by

(3) J Cl F docn 1 18 1015 10 3 S pt mbe 1958

damage to the animal s own intact thyroid gland Subsequently one lobe of a rabbit s thyroid gland was removed and thyroglobulin prepared from it was injected into the same animal s footpad Circulating antibodies were found in most animals tested after about 3 weeks When the remaining lobe of the thyroid gland was removed a month later sections of the tissue were suggestive of those seen in Hashimoto s disease This surprising finding led to a search for thyroglobulin antibodies in patients with this disease Of 18 patients studied 12 had such antibodies

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The immunologic approach to Hashimoto s disease has

In retrospect the most useful indication of bacterial infection was the occurrence of rigors The most useful investigation was aspiration of the more painful joints Aspiration and culture are indicated in every patient with rheumatoid arthritis who has suddenly deteriorated especially if there has been rigor Radiologic investigation is relatively unhelpful

Of the first 7 patients 5 died Prognosis can be improved if correct diagnosis is made early and the infecting organism cultured from the blood or infected joint for sensitivity te s Appropriate antibiotic therapy must be continued until the patient recovers Because bone infection is difficult to eradicate antibiotic therapy may have to be continued for many weeks Joints and bursae must be inspected daily for collections of pus because in patients with severe rheumatoid arthritis soft tissue abscesses or pyarthroses may develop with minimal local signs of inflammation Large collections of pus may be easily missed

Collections of pus may first be treated by aspiration and local instillation of appropriate antibiotic if not readily sterilized surgical drainage is indicated

► [It may indeed be difficult to recognize the existence of a suppur ıe arthritis in a patient with rheumatoid arthritis Such problems may become more frequent because of intra articular injection of steroids—Ed]

AUTOIMMUNE DISEASES

Review of Autoimmunization in Hashimoto s Disease According to Charles A Owen Jr[3] (Mayo Clinic) probably the most interesting development in the field of thyroid studies since the discovery of triiodothyronine is the finding of an antibody to thyroglobulin in the serum of certain patients with struma lymphomatosa (Hashimoto s disease) The discovery was the outcome of two independent lines of research one in America and one in Britain

The American investigators first obtained isoantibodies by sensitizing one rabbit to the thyroglobulin of another using improved technics of sensitization and measurement of the antibody titer Further considerations suggested that production of true autoantibodies should be accompanied by

(3) J Cl Endoc 1 18 1015 1023 S pt mbe 1958

High titer reactions (above 16) were encountered in only a few diseases such as acute viral hepatitis lupoid hepatitis primary nonobstructive biliary cirrhosis disseminated lupus erythematosus and macroglobulinemia

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DISEASES OF UNCERTAIN ETIOLOGY

Glandular Fever Field Study F G Hobson Barbara Lawson and Mary Wigfield report results of a field study made in the Oxford area lasting 30 months Of 1 156 persons examined 498 were clinically suspected of having glandular fever Laboratory studies revealed 242 patient with a positive Paul Bunnell test (group 1) and 100 with a negative Paul Bunnell test (group 2) and positive hematolgoic findings The 814 other patients were excluded from further consideration because of negative Paul Bunnell tests and doubtful or normal hematologic values The main symptoms and signs in groups 1 and 2 were so similar that on purely clinical grounds the groups could not be distinguished from one another during the stage of active disease though in group 2 the disease was less severe and recovery more rapid This was demonstrated by the fact that during the study of 79 patients hospitalized 70 were classified in group 1 and 9 in group 2

In each of the 2 complete years (1955 and 1956) there was a marked increase in group 1 cases in April May June and July There was no such seasonal incidence of group 2 cases In group 1 the age incidence rises sharply to a peak in the decade 20 29 after which it fall even more sharply whereas in group 2 the highest incidence is in the decade 0 9 with a steady fall thereafter

If a positive Paul Bunnell test is considered essential to establish a diagnosis of glandular fever (infectious mononucleosis) the present field study showed that 1 of every 3 patients clinically suspected was seronegative and failed to qualify

The infectivity of both disease states was low but the seronegative disease appeared the more infectious

(5) B M J 1 845 852 Ap 1 1958

also stimulated interest in diseases of other tissues of the body which might conceivably enter into autoimmune reactions such as autohemolytic anemias allergic encephalomyelitis rheumatoid arthritis disseminated lupus erythematosus macroglobulinemic conditions and infectious hepatitis The immunologic dogma of horror autotoxicus is undergoing thorough scrutiny

Whether the circulating antibodies to thyroglobulin found in Hashimoto s disease are related to the cause of the disease or are only the result of a still unexplained pathologic process a new avenue of research has been opened The discovery will have been profitable even if the only immediate outcome is the development of a practical accurate laboratory test for evaluation of certain diseases of the thyroid gland

► [This is currently a popular field of investigation some worthwhile new concepts should be forthcoming —Ed]

Autoimmune Reaction Against Human Tissue Antigens in Certain Acute and Chronic Diseases I Serologic Investigations Investigations have shown that it is possible to demonstrate specific complement fixation in some cases in extraordinarily high titer with human serum from patients with a number of different diseases using saline suspensions of finely homogenized normal human tissues In further work on this subject D Carleton Gajdusek[4] (Melbourne) with the technical assistance of Lois Larkin prepared antigens from normal human tissue—liver kidney skeletal muscle cardiac muscle spleen pancreas thyroid adrenal prostate lung stomach skin peritoneum aorta and pulmonary artery—and studied serums from 496 normal and diseased persons

Of the serums from 339 control subjects (187 normal and 152 with miscellaneous diseases) 3, reacted with liver and 10% with kidney antigens Positive reactions were significantly more frequent in serums from the 157 patients who could be classified under four nosologic categories of disease hepatic collagen para proteinemia or miscellaneous unrelated di ases These positive reactions occurred mainly in association with diseases for which immune mechanisms of pathogenesis have long been suspected

(4) A M A A ch I I Med 101 9 29 Jan a y 1958

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(5) Brit M J 1 845 8 Ap 12 1958

Large Epidemic Outbreak of Vomiting Associated with Meningism and Exanthem Clinical and Epidemiologic Observations I Ash[6] observed a sharp epidemic outbreak of an obscure infection believed to be caused by a virus In mild cases vomiting was the most prominent symptom The usual history was that of a child becoming sick suddenly at school or waking at night or in the early morning and vomiting in bed The main symptoms were severe headache usually moderate pyrexia rarely reaching 103 F neck and back rigidity in many cases photophobia and abdominal pain The white blood cell count was usually normal In 9 hospitalized patients who had lumbar punctures the protein was occasionally increased and the cell count varied from 27 to 2 500/cu mm

Children and young adults were mainly affected Infectivity was high and multiple cases in families were common The incubation period was about 2 days

Most cases were mild and resembled epidemic nausea and vomiting (winter vomiting disease) The common features were short incubation period precipitate vomiting abdominal pain anorexia headache injected fauces and occasional diarrhea It has been known as a definite syndrome since 1929 In the more severe cases in the present epidemic the condition resembled nonparalytic poliomyelitis because of the diphasic character cerebrospinal fluid findings and other clinical features

► [One frequently hear mention of epidemics like this among school children but they are seldom carefully studied or described —Ed]

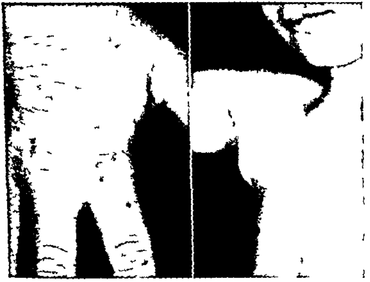
Cat Scratch Disease J D Reid[7] (Wellington Hosp) tested 116 patients with two different antigens A positive reaction to one or the other or both antigens was obtained in 40 patients The highest incidence of positive skin tests (55%) occurred in patients with lymphadenitis following cat scratch and the lowest (15 3%) in patients with miscellaneous diseases When all positive tests were considered it was found that of 30 patients on whom adequate information was available 22 (73%) had associated with cats

Clinical manifestations (Figs 13 and 14) did not differ from accepted patterns No cat scratch encephalitis was seen A prolonged duration of debility with recurrent node enlargement for 12 months was noted in a boy 9 who had

(6) B [illegible] M J 1 316 318 F [illegible] 1959
(7) N Zeala d M J 58 37 44 F b [illegible] y 1959

intestinal obstruction due to ileal intussusception with prominent lymphoid tissue in the wall of the gut and firm enlarged mesenteric nodes Skin test was strongly positive

Failure to obtain a positive skin test in clinically suggestive cases and positive tests obtained from one antigen only suggest the possibility of different strains of the causal organism Support for this was seen in a boy 16 who had the



F g 13 (l ft) —Boy 12 w th scrat h on b d Du tion u known Many c h m k l ewh re on legs a d arm f m pet at
F g 14 (ght) —A ll ry d t f 6 day d t n Cult of nod b d a erob g w h B p y no pec h cut fl mmato y l mph den t s Cat tch k n t t l m ed ma with fla
(Courte y f R d J D New Z land M J 8 33-44 F b u ry 1959)

habit of taking a cat to bed with him and who had inguinal adenitis of 3 weeks duration with positive biopsy diagnosis of cat scratch disease negative culture of part of the gland yet negative skin tests to both antigens Not only are false negative tests thought to occur but positive tests must also be regarded as having limitations in specificity and significance

Likely the skin test will remain positive for some period following active disease and interpretation of positive results will require consideration of the clinical picture Non pecific reactions may also interfere to an unknown degree since no

control is used McGovern and associates found 10% of positive skin reactions in patients with no past or present history of the disease

Alternative diagnoses were found in only 3 of the 40 cases in which the results were positive but even then the skin test readings may have been true positives False positives in clinically classic cases are likely to be rare

Cat Scratch Fever Associated with Osteolytic Lesion is reported by Platon J Collipp and Richard Koch[8] (Univ of Southern California) Cat scratch fever is usually a nonbacterial regional lymphadenitis that occurs 1 2 weeks after a scratch by a cat The course is variable and may last for a few weeks to months The cause is as yet unknown, but is thought to be viral Complications are unusual but various conditions such as erythema nodosum encephalopathy oculoglandular syndrome peripheral neuritis thrombocytopenic purpura pulmonary infiltration and a sterile osteolytic bone lesion may be associated with the disease The last entity was observed in the following case

Boy 4 had pain in the right knee associated with low grade fever 9 days before hospitalization The pain was aggravated by walking He was treated with penicillin but pain and fever persisted Two days after onset of these symptoms a maculopapular eruption was noted subsequently a swollen cervical lymph node appeared He had often played with and been scratched by cats

On physical examination positive findings included a fading erythematous maculopapular rash a firm slightly tender left anterior cervical lymph node 3 cm in diameter a mild limp favoring the right leg and slight pain on full abduction of the right hip The cat scratch skin test produced 2 cm of induration and 4 cm erythema after 2 days

By the 17th hospital day the cervical lymph node became fluctuant and was surgically drained Thick yellow pus which was sterile on routine fungous and acid fast cultures was obtained Cat scratch skin test antigen prepared from the remainder caused a strongly positive reaction when tested in a patient with known cat scratch fever

Lymphadenitis gradually subsided but the patient continued to limp On the 28th hospital day x rays revealed an osteolytic lesion in the right femoral intertrochanteric area with slight periosteal reaction along the medial aspect A needle biopsy of the lytic area revealed several granulomas with central necrosis surrounded by epithelioid cell and lymphocytes compatible with cat scratch fever Subsequent x rays revealed new bone formation about the lesion During the next 5 months the gait returned to normal and x rays showed progressive healing of the lytic area

The mild general illness sterile culture at biopsy and histologic ap

(8) New England J M 260 78 80 Feb 5 1959

pearance of the lesion suggested that the bony lesion was related to cat scratch fever

Circulating Antibodies in Sarcoidosis In sarcoidosis where pathologic changes may be widely distributed in the reticuloendothelial system it has been suggested that deficient production or transport of antibodies may be the cause of the well known depression of the delayed or tuberculin type of skin reaction Results of investigations of antibody production however have been conflicting

Raymond Greenwood Hugh Smellie Mollie Barr and A C Cunliffe[9] investigated antibody production in patients with sarcoidosis after artificial immunization with tetanus toxoid Tetanus toxoid was chosen because accurate and well established technics are available for assessing the antitoxin response and man does not naturally have circulating tetanus antitoxin Thus the effect of primary immunization could be studied in subjects who were for practical purposes in an identical immunologic state Some patients had been previously immunized in the armed forces This investigation therefore differed from earlier work in that it was possible to study separately the effects of primary immunization and of reinoculation

Results showed that after primary immunization the antibody response of patients with sarcoidosis was poorer than that of controls Perhaps the impaired response is due to partial replacement of the reticuloendothelial system by abnormal tissue Depression of the delayed types of allergic skin response is a feature common to sarcoidosis and reticulosis Both phenomena may be due to altered function of the reticuloendothelial system but it is as yet unknown whether the depression is related to impaired production of antibody

Wegener s Granulomatosis A Aubin L Duperrat and J J Debain[1] (Paris) report a case which was carefully observed throughout its course

Man 50 was hospitalized with severe progressive rhinopharyngitis and sinusitis present for 18 months and deterioration in general health Marked nasal suppuration and complete obstruction was followed by perforation of the septum and a Caldwell Luc operation was done for maxillary sinusitis Later a purulent middle ear infection developed and polyps were removed from the right nasal fossa More recent symptoms were fever (temperature around 101 F with a peak

(9) B t M J 1 1389 1391 J 14 1958
(1) P m l 66 713 715 Ap 23 19 8

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The mild general illness sterile culture at biopsy and histologic ap

(8) New England J Med [illegible]60 [illegible]8 [illegible]80 Feb 5 1959

available Two hypotheses are that these patients usually have received massive complex and prolonged antibiotic treatment for nasosinus lesions which possibly produces periarteritic lesions by sensitization or perhaps the prolonged nasosinus infection causes the hyperergic reaction of the vascular system

Diagnosis rests on the principle that in any nasosinus hemorrhagic suppuration with a rapid change in general health and phagedenic extension systematic search should be made for pulmonary and renal lesions which are sometimes latent

In many respects Wegener s granulomatosis differs from Stewart s malignant midfacial granuloma it is found in equal incidence in both sexes the acute febrile course begins with bilateral nasal suppuration and extends to the septum palate tongue and larynx and reaches the lung and even the kidneys ending in death in 4 18 months with histologic findings of perivascular lesions It is tempting to classify Wegener s granulomatosis as a particular type of periarteritis nodosa but this is not quite logical In Kussmaul s disease extraordinary naso inus necrosis extending gradually and without remission has never been observed

► [An excellent description of the clinical picture known a Wegener s granulomato is Some people prefer to look on this syndrome as a form of periarteritis nodosa however the massive involvement of the nasal cavity and paranasal sinuses seems sufficiently unique to justify a separate category —Ed]

Possible Relationship of Etiocholanolone to Periodic Fever Periodic fever has been an enigma to clinicians since it was first described Philip K Bondy George L Cohn Walter Herrmann and Kenneth R Crispell studied 2 patients with periodic fever and found an apparently specific abnormality of etiocholanolone metabolism

CASE 1 —Physician 34 had a 26 year history of periodic fever with chills lethargy anorexia malai e depression headache muscle pain and weight lo s Temperature during attacks ranged from 100 to 106 F and was u ually accompanied by leukocytosis Investigations for diagnosis of the fever had always been negative and antil iotics produced no change except when a specific infection was present

In December 1956 when he v as seen because of malaise anorexia marked fatigue and salt craving studies of adrenocortical function revealed urinary 17 ketosteroids ranging from 23 to 40 mg /24 hours an l a fasting plasma 17 hydroxycorticoid level of 20 µg /100 ml with no response to 25 mg ACTH injected intravenously over 4 hours In

( ) Y l J Bi l & Med 30 395 405 J 1958

of 104 F) painful dysphagia hoarseness leading to aphonia and diffuse severe headache At examination the entire nasal pyramid appeared tumid and the nasal root was widened by a red swelling Severe pain was felt in the bone and ascending branch of the right superior maxilla The cartilaginous septum and inferior horns had completely disappeared The nasal fossae had become a cloaca filled with crusts and thick bloody greenish pus The bony septum was ulcerated the upper portion was heaped with hard red bleeding polypoid masses especially on the right The process extended to the pharynx and larynx

These findings suggested Wegener s granulomatosis Delta-cortisone (30 mg /day) was given with immediate reduction in temperature and rapid improvement in the general condition Additional studies indicated no glomerular nephritis but moderate disturbance in the tubules

The patient lived for 6 months after admission (2 years after initial signs) survival being attributed to delta cortisone Each time the drug was stopped or the dose decreased fever increased and the lesions became more extensive The course was marked by exacerbations and remissions of functional and general signs but the lesions progressed inexorably Death occurred immediately after a rise in temperature to 104 5 F and a severe nasal hemorrhage At autopsy foci of necrosis were found in the lungs and the kidneys appeared variegated because of ischemic zones Microscopically the glomeruli showed lesions progressing from simple congestion to cellular exudate with pyknotic nuclei and fibrinoid necrosis

Wegener s granulomatosis affects adults of both sexes aged 30 60 who almost always are healthy with no previous illness and are exceptionally allergic Onset is usually marked by suppurative rhinitis and bilateral pansinusitis The apparently ordinary rhinitis tends to crust formation accompanied by obstruction and hemorrhages Examination reveals extensive necrosis leading to early perforation of the septum At this stage curettage of the maxillary sinuses is often performed The lesions extend gradually toward the palate and mouth pharynx and respiratory tract descending to the glottis and even beyond Invasion of the orbit is evidenced by chemosis and exophthalmos Pulmonary lesions usually are discovered radiologically and are extremely variable—sometimes infiltration of an entire lobe sometimes only in spots Subacute development of large cavities is pathognomonic After the lungs the kidney is most often affected

The disease displays inexorable progression and always ends in death after 4 48 months (average about 12 months) No satisfactory explanation of the pathogenesis is yet

symptoms of periodic fever may be produced by release into the blood stream of endogenous unconjugated etiocholanolone This hypothesis is further supported by the observation that adrenocorticotropin aggravates the symptoms whereas corticosteroids such as cortisone or prednisone ameliorate them Perhaps the patients suffer from an episodic inability to conjugate the steroids associated with an increased production of etiocholanolone in preference to androsterone as an end product of androgen reduction

Clinical Syndrome Variously Called Benign Myalgic Encephalomyelitis Iceland Disease and Epidemic Neuromyasthenia L D Acheson[3] (State Univ of New York New York City) describes 14 outbreaks of a paralytic illness of world wide distribution 12 of which had so many epidemiologic and clinical features in common that there is a *prima facie* case for a single or related group of causative agents

The epidemiologic features are a high attack rate a predilection for residential communities a prevalence in women a tendency to occur more commonly in young adults and the commencement of most outbreaks in the summer months The disorder is probably an infection spread by personal contact

In severely affected patients after an acute or subacute onset with headache symptoms of a gastrointestinal or upper respiratory upset muscular pains and low or absent fever an unusual type of paresis develops which is rarely associated with the classic signs of lower motor neuron or pyramidal tract involvement This is often accompanied by paresthesias sometimes by sensory loss and occasionally by painful muscular spasms myoclonus or other types of involuntary movement As the patient recovers from the paresis a curious jerky muscular contraction on volition is sometimes noted The cranial nerves and bladder may become involved

Convalescence may be prolonged by fatigue and recurring myalgia but recovery is usually complete within 3 months In a proportion varying from outbreak to outbreak a well defined state of chronic ill health develops characterized by fluctuating myalgia and paresis partial remissions and exacerbations and depression emotional lability and lack of concentration The major differences within the group of

(3) Am J M d 6 56+595 Ap 1 19 9

November 1957 he was hospitalized with another episode accompanied by temperature spikes of 2 5 days duration relieved only by cortisone Laboratory studies revealed leukocytosis (20 000 30 000) but numerous other tests including multiple cultures serologic test and searches for parasites and lupus erythematosus were negative Lymph node and liver biopsies were negative

CASE 2—Man 44 had repeated attacks every 3 4 weeks of fever vague epigastric distress anorexia and cough which lasted 3 4 days His father and brother had similar symptoms which were never completely investigated Results of physical examination were within normal limits The white blood cell count was 13 600 Repeated cultures skin tests and agglutinations for a wide variety of infectious agents were unrevealing

Studies of steroid metabolism showed less than 0 3 µg /100 ml of the glucuronides of tetrahydrocortisone and tetrahydrocortisol in the plasma in Case 1 during the febrile phase The level of the total 17 ketosteroid sulfate was less than 2 µg /100 ml in the febrile plasma In Case 2 during the febrile phase no 17 ketosteroid sulfates or glucuronides were detectable in the plasma Paper chromatography recovered etiocholanolone from the nonconjugated steroid area The crystalline material obtained by sublimation from the area corresponding to etiocholanolone on the chromatogram was conclusively identified as etiocholanolone by spectrophotometry

In Case 1 during the afebrile phase four major peaks were found in the urine androsterone etiocholanolone 11 oxy 17 ketosteroids and Δ 9 11 desoxy 17 ketosteroids The febrile phase revealed only one main peak etiocholanolone

In both cases etiocholanolone was found in the plasma at the time of the symptoms of periodic fever In Case 1 no free etiocholanolone was found during a period when symptoms were absent The demonstration of nonconjugated etiocholanolone is particularly significant since normal persons have 17 ketosteroids in the plasma only in conjugated form It is therefore reasonable to suggest that the presence of unconjugated etiocholanolone in the plasma of these patients may be associated in some way with the episodes of fever malaise headache nausea myalgia and prostration

According to a report in the literature intramuscular injection of etiocholanolone to normal subjects produced shaking chills followed by muscular aches and pains anorexia sweating headache and fever as high as 103 F Leukocytosis with a shift to the left also occurred It seems likely that the

SIMPLE TREATMENT

Fecal Enema as Adjunct in Treatment of Pseudomembranous Enterocolitis is discussed by B Eiseman W Silen G S Bascom and A J Kauvar (Univ of Colorado) There appear to be two general types of necrotizing enterocolitis one precipitated by intestinal obstruction shock or impairment of intestinal vascular supply and the other caused purely by an overwhelming Micrococcus pyogenes (staphylococcus) enteritis A number of these cases bear no relation to surgical procedures Although pure cultures of M pyogenes are found in the stools in many of the patients this is not an invariable finding Most of the recently reported cases have followed the use of oral broad spectrum antibiotics suggesting that the intestinal flora was thus altered to permit an overgrowth of antibiotic resistant M pyogenes within the gut

The author attempted to re establish the normal intestinal bacterial flora by the administration of normal feces into the colon of patients with the disease It was thought that reintroduction of the bacteria viruses and bacteriophage normally found in the colon might re establish the balance of nature with subsidence of staphylococcic predominance and the distressing symptoms caused thereby A case is illustrated

Man 65 underwent subtotal gastrectomy with a tube duodenostomy for an acute perforating bleeding and obstructing duodenal ulcer The disease course was uneventful until the 5th postoperative day at which time peritonitis developed Exploration revealed no leakage around the duodenostomy tube Next day the patient began having frequent loose mucoid greenish bowel movements On the 4th postoperative day he suddenly went into shock Smears and cultures of stool at this time revealed Staphylococcus aureus Two fecal retention enemas were given followed by a third the next day using donor feces from a normal subject who had received no antibiotics for month The diarrhea stopped within 48 hours and the stool contained no M pyogenes 4 days after the first enema

This treatment was given to 4 patients severely ill with pseudomembranous enterocolitis In each case the clinical course improved and hemolytic coagulase positive Staph aureus which had been found in large numbers in the stool disappeared following therapy

(5) Surgery 44 854 859 November 1958

outbreaks lie in the incidence of lymphadenopathy paresis and mild lymphocytosis in the cerebrospinal fluid

Clinical laboratory studies have on the whole proved unhelpful Except for two outbreaks in which a mild lymphocytosis was found the cerebrospinal fluid was normal in 95 % of the patients In two outbreaks and some sporadic cases an unusual electromyographic pattern was observed

No deaths directly attributable to the disease have occurred and the pathology remains unknown No known bacterial or viral pathogen has been incriminated Outbreaks can be distinguished on clinical grounds from poliomyelitis encephalitis lethargica the arthropod borne encephalitides epidemic myalgia and infectious mononucleosis The disorder is not a manifestation of mass hysteria

Possible Infectious Etiology of Multiple Sclerosis Harry B Harding Lewis J Pollock Norman Dobin and Daniel Ruge[4] (Northwestern Univ) in a controlled study begun in 1951 attempted to discover whether multiple sclerosis is caused by a transmissible agent Specimens were examined from 38 patients with multiple sclerosis and the fluids and tissues of 2 patients who died during their illness Animal inoculations culture mediums tissue culture technics and chick embryo inoculations were all negative The material was passed to 20 monkeys 70 adult mice 242 suckling mice 6 hamsters 174 chick embryos and 20 male rabbits

Passage was also attempted in 448 tubes of culture mediums designed to support the growth of micro organisms of the genera borrelia and leptospira Attempts were made to infect 500 tubes of HeLa cell and monkey kidney cell tissue cultures Also a serologic survey was conducted in 68 persons with the clinical diagnosis of multiple sclerosis using viral rickettsial spirochetal Wassermann Kahn heterophil antibody and cold agglutinin antigens

The results did not support the concept that an infectious agent is involved in the cause of multiple sclerosis

► [This was a long piece of investigation which needed to be done because so many people have reported findings tending to implicate a virus or other micro-organisms as the cau e of multiple sci cosis —T J]

(4) Qua t B ll N thw t rn Un M S hool 3 338 352 W te 1958

THE CHEST

CARL MUSCHENHEIM M D

PART II

THE CHEST

PULMONARY FUNCTION

► The grouping of the following papers under the heading Pulmonary Function perhaps requires some explanation because few of them are studies purely of pulmonary physiology and several are concerned with a specific disease such as emphysema to which another section is assigned and in which these might alternatively be included The reason for this special grouping is that these studies whatever the disease each is most concerned with are directed toward the elucidation of fundamental mechanisms This is not to say they are theoretical or devoid of practical implications nor that papers on related subjects included elsewhere in the section are of less fundamental importance It is rather that this group is concerned more with unsettled question and new methods (or both) which are related particularly to the understanding of pulmonary function The order of presentation also requires comment since there are so many points of relation as well as of conflicting views or evidence among them It has not been possible to arrange these studies in a sequence which would bring out all the relationships seriatim nor does an elaborate system of cross references in editorial comments seem practical The editor thus feels constrained to rely to point out that this will not be easy reading but that the attentive reader may find less to confuse him if he bears in mind when reading the tenth abstract for instance much of what he has read in the fourth and the sixth —Ed

Case of Chronic Mountain Sickness in the United States Clinical Physiologic and Electrocardiographic Observations Chronic mountain sickness (Monge s disease) is observed in persons residing at high altitudes and is characterized by the appearance of intolerance to the lowered oxygen tension in a previously acclimatized person This results in polycythemia and produces a group of symptoms resembling those of true erythremia (easy fatigability headache paresthesia and fullness) Cyanosis deepens in time and periods of unconsciousness may occur sometimes ending in coma These abnormalities disappear when the patient moves to sea level

Hans H Hecht and John H McClement[1] (Salt Lake City) report a case of this condition

Man 28 resident of the Colorado Rocky Mountains had spent

(1) Am J Med 25 470 477 Sept mbe 1958

rected toward correcting or alleviating the basic lung disease

Hypoventilation Syndrome in Case of Chronic Epidemic Encephalitis was studied by T Garlind and H Linderholm[3] (Karolinska Hosp Stockholm)

Man 45 who had epidemic encephalitis 34 years ago had postencephalitic parkinsonism He had cyanosis some symptoms indicating cardiac or pulmonary disease and polycythemia Hypoventilation was

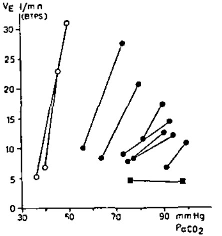


Fig 15 — V t l t on l t t P d g b th g f 100% O 1 5 7% CO n O V t l t rv po t CO th h p t ent (w l 1 sq) m d w h 7 p t t w h mphysem (sol d 1) w th I d g b eath g 100% yg f m l g t d th t en d w th 2 n m l b ject (1) (C rt y f G l d T a d L d h lm H A t med sc 1 16 333 349 1958)

present resulting in hypoxemia and hypercapnia and increased bicarbonate content of the blood

The patient s response to carbon dioxide was compared with that of some patients with emphysema with carbon dioxide retention of similar degree and with 2 normal subjects (Fig 15) All with emphysema had increased ventilation with increasing Pa_{CO} but the study patient showed slightly lower ventilation during carbon dioxide inhalation when Pa_{CO} increased Therefore the high Pa_{CO} or high bicarbonate content of the blood per se does not explain the unresponsiveness of the respiratory center Oxygen saturation of the arterial blood during work remained at the same level as at rest Disturbed regulation of ventilation due to de

(3) Act m d sc 1 16 333 349 1958

most of his life at an altitude of 10 000 ft He fulfilled Monge s criteria for chronic mountain sickness although the altitude was lower than that associated with true Monge s disease He had marked erythrocytosis and moderate to severe arterial oxygen unsaturation at all times which was not corrected at sea level Even after the patient had resided in Los Angeles for 2 years and was asymptomatic disturbed pulmonary gas exchange was evident from the elevated venous al mixture component and the reduced oxygen diffusing capacity at rest Pulmonary artery pressures and pulmonary arteriolar resistance were always slightly elevated

It is suggested that some cases of chronic mountain sickness may result from disturbances in respiratory gas exchange and altered ventilation perfusion ratios on the basis of intrinsic pulmonary disease too mild to cause signs or symptoms at sea level

► [This observation that a functional derangement under adverse circumstances may result from disease too mild to be apparent under normal circumstances is made also in the following paper in connection with the pulmonary disturbances of obesity —Ed]

Pulmonary Function in Obese Persons George N Bedell William R Wilson and Paul M Seebohm (State Univ of Iowa) studied 28 persons who weighed at least 100 lb more than the ideal weight Normal arterial oxygen saturation was found in 13 and hypoxemia in 15 10 of the latter had alveolar hypoventilation as manifested by increased arterial Pco Alveolar hypoventilation was associated with myxedema or lung disease

The obese persons with normal arterial oxygen saturation had reduced expiratory reserve volumes reduced maximal breathing capacities and reduced maximal flow rates When they lost weight their lung function returned toward normal

Some obese persons without lung disease had arterial hypoxemia without hypercapnia This is believed to be due to disturbance in ventilation perfusion ratios in the lungs However when alveolar hypoventilation is present (arterial hypoxemia and hypercapnia) intrinsic lung disease a disturbance of the respiratory musculature or a central nervous system lesion should be suspected

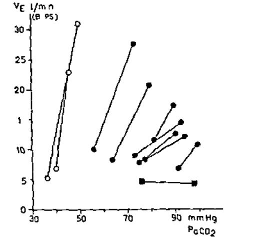
The obese persons with normal lungs normal respiratory muscles and an apparently normal respiratory center had no alveolar hypoventilation Most obese persons with pulmonary insufficiency are benefited by weight loss Presumably the improvement is caused by reduction in the work of breathing Obese persons with lung disease need therapy di

( ) J Clin I 37 1049 1060 J 1 1958

rected toward correcting or alleviating the basic lung disease

Hypoventilation Syndrome in Case of Chronic Epidemic Encephalitis was studied by F Garlind and H Linderholm[3] (Karolinska Hosp Stockholm)

Man 45 who had epidemic encephalitis 34 years ago had postencephalitic parkinsonism He had cyanosis some symptoms indicating cardiac or pulmonary disease and polycythemia Hypoventilation was



F g 15 —V t l t n l t t P d g b ath g f 100% O a d 5 7% CO O V t l t p t CO th th p t (sol d sq) m d w th 7 p t w th physem (l d cl) w th P d g b th g 10 ~ yg n f m l l th pat ent d w th 2 norm l b ject (1) (C urte y f G l d T d L d h lm H \ t m d sc d 16 333 349 1958)

present resulting in hypoxemia and hypercapnia and increased bicarbonate content of the blood

The patient's response to carbon dioxide was compared with that of some patients with emphysema with carbon dioxide retention of similar degree and with 2 normal subjects (Fig 15) All with emphysema had increased ventilation with increasing Pa_{CO} but the study patient showed slightly lower ventilation during carbon dioxide inhalation when Pa_{C} increased Therefore the high Pa_{CO} or high bicarbonate content of the blood per se does not explain the unresponsiveness of the respiratory center Oxygen saturation of the arterial blood during work remained at the same level as at rest Disturbed regulation of ventilation due to de

(3) A t m d l 162 333 349 1958

most of his life at an altitude of 10 000 ft He fulfilled Monge s criteri for chronic mountain sickness although the altitude was lower than that associated with true Monge s disease He had marked erythrocy tosis and moderate to severe arterial oxygen unsaturation at all times which was not corrected at sea level Even after the patient had re sided in Los Angeles for 2 years and was asymptomatic disturbed pulmonary gas exchange was evident from the elevated venous ad mixture component and the reduced oxygen diffusing capacity at rest Pulmonary artery pressures and pulmonary arteriolar resistance we e always slightly elevated

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( ) J Clin I v t 37 1049 1060 J ly 1958

274% (mean 183%) The total mechanical work of breathing tended to be less in patients with pulmonary emphysema than in normal subjects whether expressed as work per liter of ventilation or work per minute This might be expected because about 63% of the work of breathing is performed in overcoming elastic resistances and substantial loss of lung elasticity occurs in emphysema Though the total mechanical work done on the lungs and thorax tends to be less at low ventilations in patients with emphysema than in normals

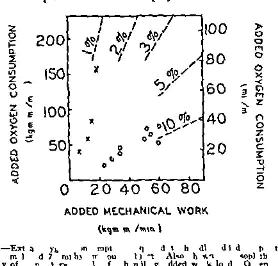


Fig 16—Ext a ys n mpt η d t h dl d i d p tory w k load 9 m l d 7 mj bj π ou t) t Also h wn sopl th p se t g ffi y of p t ry l f h nil g dded w k lo d O ep t n mal bj ct Y p es t mphy m tou t) t (C ı t Ch k R M J Cl In t 38 494-499 M ch 1959)

the oxygen cost of breathing is 4 5 times greater because of the greatly reduced efficiency of the respiratory muscles In emphysema with increases in ventilation there is disproportionate increase in oxygen consumption of the respiratory muscles This may help to explain the disability present in pulmonary emphysema and the inability of the severely emphysematous patient to meet the increased energy demands of exercise and infection

It is suggested that use of closed circuit technic yields values for oxygen cost of breathing and efficiency of the respiratory muscles that are comparable to those obtained by open circuit technic Values obtained for oxygen consumption or efficiency of the respiratory muscles for handling

creased or absent sensitivity of the chemoceptors of the respiratory center with remaining respiratory reflexes regulating respiration during hypoxia and during exercise was thought to be the most probable explanation for the condition.

The polycythemia, increase in hemoglobin concentration, total amount of hemoglobin and blood volume were thought to be secondary to the chronic hypoxia. The big heart was increased in proportion to the increase in blood volume and total hemoglobin.

Heart catheterization showed filling pressures of the ventricles in the normal range. The stroke volume was normal in relation to blood volume and heart volume. High pulmonary arterial pressure and pulmonary vascular resistance disappeared during hyperventilation and during breathing of 100% oxygen.

Oxygen transport was maintained with normal oxygen saturation and oxygen tension of mixed venous blood despite the arterial hypoxemia due to increase in hemoglobin concentration of the blood and slightly high cardiac output. Adaptation of the patient to the low alveolar oxygen tension was similar to that found in residents at high altitudes.

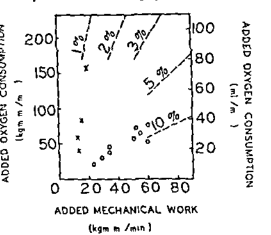
Oxygen Consumption and Efficiency of Respiratory Muscles in Health and Emphysema were studied by Reuben M. Cherniack[4] (Univ. of Manitoba). In normal subjects oxygen consumption of the respiratory muscles was 0.45-1.87 ml./L. of ventilation (mean 1.16) and in emphysematous subjects it ranged between 1.68 and 18.50 ml./L. of ventilation (mean 5.96). In normal subjects oxygen cost of increase in ventilation of 30 L./minute above resting ventilation was below 2 ml./L. In those with emphysema, oxygen cost was high for even slight increases in ventilation and rose further when ventilation was increased.

The extra oxygen consumption associated with added work loads in 9 normal and 7 emphysematous subjects is shown in Figure 16; extra oxygen consumption per unit of added work load was greater in the emphysematous patients than in the normals.

Efficiency of the respiratory muscles of normal subjects ranged between 7.20% and 11.10% (mean 8.58%), whereas in the emphysematous subjects it ranged between 1.24% and

(4) J. Clin. Invest. 38:494-499, March 1959.

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F g 16—E t a en on mpt q d t h dl 11 d p a y w k l ad 9 o m l d 7 phy m b t Al h wn e so leth p se t g effi e y f e p tory m l for h dl g added w k load O ep t m l bject X p ese t mphy m t1 (C t t Ch k R M J Cl I v t 38 494-499 M ch 19 9)

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(4) J Cl In t 38 494 499 Ma h 1959

becomes the dominant problem These patients have little respiratory reserve and infection often precipitates acute pulmonary decompensation Hypoventilation results in high arterial CO_2 tension acidosis and low oxygen saturation Increase of ventilation is the primary objective of treatment in these patients

Observations on Control of Respiration in Emphysema Effects of Oxygen on Ventilatory Response to CO_2 Inhalation D W Richards H W Fritts Jr and A L Davis[6] (Columbia Univ) analyzed performance of the respiratory center according to the schema shown in Figure 17 For this analysis the elements composing the effector limb of the

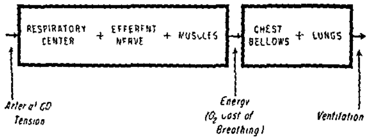


Fig 17 Schema for analyzing performance of the ventilatory apparatus (C rt f R ha d D W t l T A A Phy s 71 14 151 1958)

ventilatory apparatus were divided into two boxes the left hand box contains the respiratory center nerves and muscles The right hand box contains the chest wall and lungs Performance of the left hand box is characterized by determining the extra energy used by the respiratory muscles for a particular increment in the arterial blood P_{CO_2} performance of the right hand box is characterized by measuring the extra ventilation realized per increment of energy consumed

The authors studied 9 patients with hypercapneic emphysema and 8 normal subjects who served as controls The emphysematous patients breathed various gas mixtures containing 0-5% CO_2 whereas the controls breathed mixtures containing 0 7% concentrations of this gas By measuring oxygen uptake at each level of ventilation estimate of the oxygen cost of breathing was made Arterial blood samples were also collected and analyzed for oxygen saturation pH

(6) T A Am Phy n 71 142 151 19 8

added work loads depend on the resistance offered by the apparatus used The values derived by the authors therefore are not absolute but do serve to distinguish distinctly between normal and emphysematous subjects

Rapid Diagnosis of Ventilatory Failure with Carbon Dioxide Analyzer is described by Donald E Griggs Jack D Hackney Clarence R Collier and John F Affeldt Ventilatory failure is often overlooked because it is difficult to diagnose by symptoms or physical examination

METHOD—A Liston Becker (model 16) CO_2 analyzer is set up for the rebreathing method The patient rebreathes from a small rubber bag previously filled with CO_2 of known concentration usually 8% CO_2 in air but in patients with respiratory failure higher concentrations of CO_2 must be used In 4-6 breaths the concentration in the bag in the lungs and in the mixed venous blood comes into equilibrium The rebreathed gas is constantly being drawn through the analyzer from the system and the mixed venous CO_2 concentration is directly recorded The arterial CO_2 tension is calculated

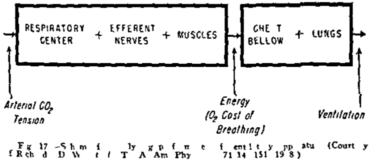
This test can be performed at the bedside by a technician and results obtained in 5 10 minutes It can be repeated frequently does not require arterial puncture or blood gas analysis and can be made on confused or comatose patients The authors used this rapid CO_2 analyzer service to determine the ventilatory status of over 600 patients and found ventilatory failure in many conditions including paralytic poliomyelitis cerebrovascular accidents infectious neuronitis myasthenia gravis progressive muscular atrophy porphyria scleroderma insecticide poisoning barbiturate poisoning marked obesity with polycythemia postthoracotomy deformity pulmonary fibrosis thoracic scoliosis asthma with excessive sedation and emphysema In many of these patients diagnosis of ventilatory failure was not considered at first but when thought of was easily established with the aid of the CO_2 analyzer service Not until after the ventilatory failure was treated did the patients improve In many instances these patients were being treated for intractable congestive heart failure while ventilatory failure was really their chief problem

The authors studied 20 patients with emphysema who had definite clinical evidence of cor pulmonale All showed decreased ventilation with CO_2 retention (arterial P_{CO_2} over 5 mm Hg mean P_{CO_2} 62 5 mm Hg) In emphysema as the disease advances hypoventilation with ventilatory failure

(5) Am J Med 25 31 3(July 1958

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(6) T A Am Phy n 71 142 151 1958

and P_{CO_2}. It was found that the altered mechanical properties of the lungs played an important role in reducing response to CO_2 in patients with emphysema. By way of contrast, response of the respiratory center and muscles measured in terms of effort appeared similar in the controls and in the patients.

In investigating the effect of altering the arterial blood oxygen tension on response to CO_2, the following protocol was adopted. Each subject was studied during four 20 minute breathing periods with each period separated by 15 minute intervals of rest. In a sequence fixed by a table of random numbers the subject breathed 21% O_2, 3% CO_2 in 21% O_2, 50% O_2 and 3% CO_2 in 50% O_2. At the 14th and 16th minutes of each breathing period ventilation was measured and samples of arterial blood were drawn and analyzed for oxygen saturation, pH and P_{CO_2}. Response of the respiratory center and muscles was judged by measuring the minute ventilation.

Two groups of emphysematous patients were studied: arterial blood CO_2 tensions were normal in group 1 but in group 2 ranged from 43 to 55 mm. Hg at rest. Mechanically patients in group 2 were much more seriously affected with greatly reduced ventilatory capacities; the diminished ventilatory response was probably due largely to the increased effort required to ventilate the lungs.

In patients with emphysema the increased effort of breathing plays an important part in reducing response to CO_2.

Induction of Respiratory Acidosis by Oxygen Breathing. Respiratory acidosis in emphysematous patients is precipitated by respiratory infection, anesthesia, narcotics and sedatives or by administration of high concentrations of oxygen. The last factor has made many physicians reluctant to administer oxygen to a dyspneic emphysematous patient. To combat this therapeutic paradox, various regimens have been used, such as administration of oxygen by mask or nasal catheter for 20-30 minutes followed by breathing of room air for a similar period. Oxygen has also been recommended at flows of 1-2 L./minute, to be increased after elapse of a certain length of time for adaptation. Others believe that lower concentrations of oxygen (30-40%) can relieve anoxia without producing respiratory acidosis. Still others believe that the ideal way to administer oxygen safely in these cir

cumstances is with the assistance of a mechanical aid to ventilation

In most previous work on respiratory acidosis little has been done to assess the level of impairment of pulmonary ventilation below or above which respiratory acidosis may or may not be precipitated by high oxygen concentrations It i common clinical experience that such a situation usually pertains only to severe respiratory cripples who are very hypoxic hypercapneic and in right heart failure

Herman F Froeb Charles I Leftwich and Hurley L Motley[7] (Univ of Southern California) administered pure oxygen (99 5%) for 6 10 minutes to 209 patients with impairment of pulmonary function varying from virtually none to severe The appearance of respiratory acidosis (a fall in arterial pH below 7 35) was correlated with the degree of impairment of pulmonary ventilation as measured by the maximal breathing capacity and the 3 second timed vital capacity

Respiratory acidosis was observed in 18 patients Except for 1 normal subject it appeared only in patients who had maximal breathing capacities and 3 second timed vital capacities below 40 50% respectively of their predicted values The incidence rose markedly as patients with the most severe impairment were tested Pulmonary fibrosis with or without congestion was common among the 17 in whom respiratory acidosis developed on oxygen breathing In 3 patients with emphysema respiratory acidosis of a lesser degree was produced and hypoxia wa relieved by mixtures of 30 40% oxygen

Pulmonary Capillary Proliferation Induced by Oxygen Inhalation is evaluated by Philip C Pratt[8] (Ohio State Univ) It is known that progressive alteration in pulmonary function occurs during prolonged exposure to inhalation of atmospheres containing high concentrations of oxygen In exposure over several days not only is there progressive loss of vital capacity but recovery of the original vital capacity is slow and may require several days Examination of pulmonary tissue from animals killed after days or weeks of exposure to increased oxygen has revealed hyperemia engorgement and hemorrhage fibrinous pneumonia and congestion and damage to capillary walls

(7) Am R T be 77 737 748, M y 19 9
(8) Am J Path 34 1033 1049 No Dec 19 8

Pratt found evidence that with oxygen inhalation for as little as 2 days pulmonary alterations consisting of capillary congestion and proliferation may be observed After continuous inhalation for about 2 weeks diffuse fibrosis was noted Alveolar concentrations of oxygen obtained during administration by nasal catheter are believed sufficient to cause these alterations

Pulmonary changes induced by oxygen often have been erroneously considered to be manifestations of certain obscure pulmonary diseases Thus capillary proliferation has been mentioned in many publications on the Hamman Rich syndrome Similar lesions have been described in other chronic progressive pulmonary disorders characterized by respiratory insufficiency Because most patients with these conditions receive oxygen therapy during the final stages of their ailments the likelihood that septal capillary proliferation may reflect oxygen inhalation requires consideration So called plasma cell pneumonia of premature infants is said to be characterized by generalized septal thickening without clinical or morphologic evidences of infection but with progressive pulmonary insufficiency This may also be a manifestation of oxygen toxicity

There are various reasons why in certain patients no capillary changes develop even though they are exposed to oxygen inhalation Among these is that because of technical reasons or shallow respirations administration of the gas may not actually have appreciably raised the pulmonary oxygen concentration Another possible explanation is that oxygen has more pronounced effect when given to the normal person than to the patient with a pathologic state accompanied by hypoxemia

Studies on Regional Analysis of Pulmonary Ventilation and Circulation with Aid of Isotope Thoracography and Selective Pulmonary Angiography were conducted by W Bolt and H Rink[9] (Univ of Cologne) In isotope thoracography performed for regional analysis of pulmonary ventilation the patient inhales a radioactive gas Xenon 133 which emits gamma rays with a half life of 5 7 days proved to be the most suitable for this purpose It does not enter into any chemical reactions in the human body The inhaled gas is registered with the Geiger Muller counter outside the thorax at 16 sym

(9) Thorax h rurg 5 3 9 390 March 1958

metrically arranged points simultaneously Thus the ventilation in 16 different lung fields can be studied at the same time and with the aid of a special registering apparatus it can be analyzed individually Recently the authors started



Fig 18—I p t ent w th c uppe h l f t be l s elect g og phy of p lmon ry sel h w on id f dec rt t (right) l y t of l w l t p lled pw d w h ffi tly p served pe ph l vasc l zat on Uppe l be rt poo ly t al ed a ea f pe fi p oc t eat d p e ou l b pn moth O l f i f l g uppe l be sel h w d fi te t oph d f gment on espec lly lat lly n ca er ou ea (C t y f Bol W d Rink H Th h ru g 5 379 390 M h 1958)

using 64 counters The amount of radiation is minimal particularly since the isotope gas is completely exhaled immediately The body tissues are first saturated with inactive xenon mixed in the inhaled air Thus radiation injury due to diffusion of active xenon is also excluded With this method it is possible to *elucidate and differentiate circumscribed func*

tional disturbances such as tumors atelectases segmental and lobar destruction of various causes and bronchopulmonary fistulas

Studies with selective pulmonary angiography revealed that segmental atelectases are reversible if angiography shows filling of the capillaries of the involved area Partial atelectases are irreversible if angiography fails to visualize the capillary filling phase Generalized deformity of the vascular network in the segmental and subsegmental angiogram is seen in processes in which parenchymal atrophy is in the foreground such as cystic pulmonary degeneration

Substantial emphysema is characterized morphologically by spreading of the vessels due to considerable loss in vascular branching especially in the periphery of the vascular system

Selective pulmonary angiography (Fig 18) is of great diagnostic importance in all conditions which affect primarily the arterial segment of the pulmonary circulation In primary pulmonary sclerosis the angiogram reveals that the diameter of the pulmonary vessels becomes suddenly smaller toward the periphery while in the normal lung fields the vessels become smaller gradually

Mechanical Properties of the Chest During Intermittent Positive Pressure Respiration were studied by Lionel H Opie J M K Spalding and F D Stott[1] in patients with paralysis or paresis of the respiratory muscles

METHOD 1—A four channel direct writing capacitance manometer was used to record simultaneously tracheal pressure esophageal pressure tracheal air flow and tidal volume Frequency response is satisfactory up to 15 c All the patients had tracheotomy and tracheal pressure was measured close to the external end of the tracheotomy tube Esophageal pressure which was used to indicate intrathoracic pressure was measured by water filled tube or air filled balloon Many patients were fed by stomach tube and in these it was convenient to attach a polyethylene tube 1 mm bore and 100 cm long to the stomach tube so that when the stomach tube was in situ the end of the polyethylene tube was about in the mide ophagus

Another method of recording esophageal pressure was used on other patients

METHOD 2—An air filled system was used which more readily gave readings of absolute pressure A polyethylene tube 1 5 mm bore was enclosed over its terminal 18 cm by a latex balloon 0 6 cm in diameter that tolerated introduction of 2 ml air when lax and free before any pressure change occurred Before records were made

(1) Lancet 1 545 550 Mar 14 1959

the balloon was emptied of air then 1 5 ml was introduced into it The part of the polyethylene tube in ide the balloon had an aperture in its wall every 2 cm Initial experience in positionin, the balloon was gained with a radiopaque marker later the balloon was passed until it was estimated that its upper end lay 2 5 cm below the level of the larynx Air flow to and from the trachea was measured by a modified Lilly grid type flowmeter Differential pressure was re corded with a Southern Instruments differential pressure head type G 247C This head was fitted with external damping resistances on both sides to achieve approximately critical damping and at the same time equalize the respon e time of the two sides Tidal volume was

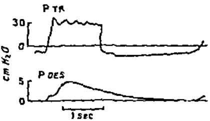


Fig 19—T h l d oph g l p e p tent w th ev b on h t d mphy m t t d w th nt mit t po t J u esp t on Neg t p f l t produ ap d p tion (Cou t sy f Ope L H t l La t 1 545 550 M 14 1953)

recorded by electric integration of the air flow signal The time con stant of the int grator was 30 seconds calibrated against a record ing spirometer of known linearity

Two subjects were studied while receiving intermittent positive pressure respiration from Radcliffe respiration pumps In both difficulty with the expiratory phase was well demonstrated and unlike the state in paralyzed patients negative pressure did not hasten expiration (Fig 19) Eso phageal pressure falls slowly In 1 patient flow was measured and again use of the negative pressure phase failed to shorten duration of the expiratory flow or to enhance the peak value reached

Recently intermittent positive pressure respiration was in troduced as treatment for severe bronchitis and emphy ema in its acute exacerbations Inspiration may be much slower but this can readily be overcome by increasing the inspira tory pressure Expiration however is notably slowed so that it may not be complete before the next inspiration This re sults in permanently raised intrathoracic pressure that may be undesirable in these patients who are often already on the verge of circulatory failure In them application of negative

pressure may be useless or even harmful owing to the trapping effect

► [This study raises important questions relative to the use of mechanical aids to respiration in emphysema in which intermittent positive pressure breathing is extensively used The magnitude of the elevation of intrathoracic pressure and its effect in impeding circulation has been dismissed by some as inconsequential even in the presence of cor pulmonale with circulatory failure This is a question however on which there have been few similar studies with all of the types of apparatus currently in use More studies of this type might serve to sharpen the indications for and improve the administration of intermittent positive pressure breathing which is a complicated method of therapy requiring painstaking supervision and close observation of the patient —Ed]

Studies on Nature of Arterial Blood Oxygen Unsaturation in Chronic Pulmonary Disease are reported by Hurley L Motley (Univ of Southern California) When the mean alveolar Po is normal a decrease in arterial blood oxygen saturation as measured in a sample from the brachial artery may be due to (1) a diffusion difficulty at the alveolar capillary membrane (alveolar capillary block) (2) shunting of blood through nonventilated areas in either the lung or heart or (3) poorly ventilated or nonventilated alveoli

The simple test of using different levels of high oxygen breathing helps to differentiate a true diffusion difficulty (alveolar capillary membrane block) from shunting at the alveolar level produced by poorly ventilated alveoli or nonventilated alveoli Breathing 100% oxygen tends to obscure multiple small areas of shunting at the alveolar level because of the high partial pressure of the dissolved oxygen in the plasma which perfuses ventilated alveoli in the smaller venules before the red blood cells become piled up as in the larger vessels of a big arteriovenous fistula

In many patients the arterial blood oxygen saturation at rest is decreased only in a slight to moderate degree but with mild exercise there is a marked drop even though emphysema is not a factor and the maximal breathing capacity is fairly good Total lung capacity is often considerably decreased in these patients yet the carbon dioxide content may be normal This decrease may be due to pulmonary fibrosis sarcoidosis asbestosis or collagen type diseases such as lupus erythematosus and pneumoconiosis

A second test to determine the nature of arterial blood oxygen unsaturation is the use of intermittent positive pressure breathing with compressed air only (no bronchodilat

(2) D Ch st 33 581 599 Ju 1958

ors) Such breathing produces an increased tidal volume in most cases with some degree of hyperventilation The increase in mean pressure for the entire breathing cycle is usually less than 5 mm Hg when the peak cycling pressure is set at 20 cm water If a significant increase in arterial blood saturation occurs with pressure breathing on air this can only be explained on the basis of improved aeration for poorly ventilated alveoli

The 12 cases presented in the table illustrate a variety of clinical conditions which show alterations in arterial blood oxygen saturation both at rest and with exercise (1 minute step up test of 30 steps on an 8 in stool) Intermittent positive pressure breathing with compressed air only and graded levels of oxygen breathing (32% and 40%) as well as 100% oxygen breathing were compared both at rest and with exercise for the effect on the arterial blood oxygen saturation A mixture of 32% or 40% oxygen does not obscure shunting at the alveolar level whereas 100% oxygen may do so especially at rest However due to alterations in perfusion ventilation relationships the hemodynamic situation with exercise is different from that at rest Thus the selective perfusion of blood through the better ventilated areas which may be present at rest no longer holds with exercise because the increased cardiac output produces perfusion through more poorly ventilated or nonventilated areas A 32% oxygen mixture increases the inspired Po over 70 mm Hg and this is more than adequate to overcome an alveolar capillary membrane block which might be present If the block were of greater magnitude than this value (alveolar arterial Po difference of 70 mm Hg) the patient would be unable to live on air breathing The use of a 40% oxygen mixture almost doubles the inspired Po as compared with air breathing It can be noted that the resting arterial blood oxygen saturation on 100% oxygen in all of the patients except 4 with large shunts and 2 with emphysema had a saturation of around 99% or more However saturation on 100% oxygen with exercise may not be normal even though it is normal at rest

With a large shunt such as an arterial venous fistula in one lobe of the lung (localized in the left lower lobe by pulmonary angiograms) as in Case 1 even 100% oxygen breathing at rest does not produce a normal saturation With multiple large arteriovenous fistulas as in Case 2 the de

Case Number		1		3	4	5	6	7	8	9	10	11	12
Diagnosis		L S AV F t l Left Lower Lobe	Multiple Large A V F tula All Lob	M ltipl Sm ll A V F tul All Lobe	Atri l S ptal D f t P lmo na y Hyper ten on	B n hiect s nd Emphy em	F br s	F b	Sa do	Lupu Eryth m t s ( )	Asbe to is	D atomite Penum con o is	Pulm ary Emphysema
Age y M(Male) F(Female)		22 (M)	40 (F)	30 (F)	32 (M)	55 (F)	66 (M)	37 (F)	3 (F)	22 (M)	58 (M)	65 (M)	57 (M)
Body Surf Area Sq M		1 69	1 59	1 79	1 0	1 6	1 96	1 59	1 44	1 93	1 60	1 65	1 66
Total Vital Capacity Per Cent Predicted		9 0	1 0 3	105 0	66 7	60 8	60	47 7	35 6	15 6	69 5	100 0	59.3
T m d V t l C p ty 3 Per Cent Predicted		79 0	112 1	98 1	58 3	45 9	60	47 7	34	15 8	56 8	8 8	33 6
Maximal Breathing Capacity Per Cent Predicted		98 0	123 0	87 1	60 0	63 6	10 3	89 8	5 9	35 4	73 7	95 7	1 5
Residual Air Per Cent Predicted		85 7	116 0	89 6	112.3	158 8	40 6	59 9	57 1	6 0	1 61	13 6	301 9
Total Lung Capacity Per Cent Predicted		80 0	115 5	98 4	72 3	81 7	55 7	50 0	40 7	4 7	74 1	109 8	1 07
R d l P Ce t Total Lung Capacity		1 0	25 1	18 2	31 1	48 7	1 9	34 5	8 0	5 6	4 5	36	63.2
V nt lat n F to P C t		30 2	111 6	98.3	6 9	63 6	95 8	0 0	60 5	9 7	63 1	87 1	31 8
Arterial Blood Oxygen Saturation Per Cent	Rest Ambient Air	89 0	64 8	87 6	85 3	92 7	93 8	96 0	87 8	8 1	93 8	9 5	85 2
	Rest IPPB Air			87 5	84 5	96 0	96 4		4 0		96 5	93 5	92 0
	Rest 32 P Cent O									5 8			94.2
	Rest 40 P Cent O		69 0	92 4	86 5								
	Rest 100 P Cent O	90 8	75 5	97	94 4	98 9	99 8	99 0	99 0	99 1	99 6	[illegible]	[illegible]

	E i Ambi t A	86 0	54 8	72 0	64 0	91 8	84 5	83 5	71 6	64.3	8..0	84 8	8 9
	E rci IPPB Air					89	–		--		89 5		
	E rc se 3 P C t O					91 3	63 6	86 8	78		90 5	0 5	91 7
	E 40 P C t O								8 5				
	E se 100 P Ca t O		54 3		63 0		3 0	96 0		80 0			
A t i l CO C t t,	R t	39 4	35 1	3 7	37 9	50 8	52 0	44 6	46 0	48	45 5	45 1	58.3
V l m P C t	E r ise	38 7	34	36 0	42 9	48 1	51 5	41 7	44 5	47 1	45 8	49 3	55.6
Arte l T D ect	pCO	28 7	2	29 0	35 4	57 6	4 1	30 5	46 9	59 1	43 9	34 8	52 1
M m t R t, mm Hg	pO	55 4	43 8	61 3	67 5	75 1	88 9	90 3	68 9	59 5	84 6	88	68 9
Al e l A t r l pO D ff r m Hg		63 0	65 0	3 0	41 7	4	4 4	19 6	1 4	4 8	5 8	9 4	14 4
T tal V t l t(	R t	5 5	6 00	3 87	6 18	2	72	3 15	3 69	8 3	3.36	4 85	4 60
L /m /sq M BSA	E rc	15 9	13 05	17 00	13 10	8 0	12 07	1 19	12 42	17 14	10 01	17 46	7 19
O yg n Uptak	R t	139	145	1 3	128	115	102	1 8	119	156	124	68	102
ml /min /sq M BSA	E se	654	324	508	64	394	443	478	371	259	403	615	48
O yg P Cent	R t	65	2 4	3 18	2 07	4 33	3 76	4 06	3 4	1 86	3 69	1 40	6
E t t d I m Ai	E	4 19	48	2 84	2 08	4 81	3 6	3	2 93	1 51	4 0	3 5	3 45
Effecti T d l A R t P C nt		7 0	50 5	77 0	50 4	56 0	57 8	85 4	59 0	36	63 0	50 4	45 0
T d l Ai ml	R t E	739 1319	625 988	5 0 1039	498 69	51 577	685 986	54 497	307 436	315 3 9	376 668	381 993	318 477

NATURE OF ARTERIAL BLOOD OXYGEN UNSATURATION IN PULMONARY DISEASE

Case Number		1	2	3	4	5	6	7	8	9	10	11	12
Diagnosis		Large AV Fistula, Left Lower Lobe	Multiple Large AV Fistula All Lobes	Multiple, Small AV Fistula All Lobes	Atrial Septal Defect, Pulmonary Hypertension	Bronchiectasis and Emphysema	Fibrosis	Fibrosis	Sarcoidosis	Lupus Erythematosus ( )	Asbestosis	[illegible]	Pulmonary Emphysema
Age, Years M (Male) F (Female)		22 (M)	40 (F)	30 (F)	3 (M)	55 (F)	66 (M)	37 (F)	3 (F)	2 (M)	58 (M)	65 (M)	57 (M)
Body Surface Area Sq M		1 [illegible]	1 9	1 79	1 70	1 6	1 96	1 59	1 44	1 93	1 60	1 75	1 66
Total Vital Capacity Per Cent Predicted		79 0	1 0 3	103 0	60 7	60 8	60 2	47 7	35 6	15 6	69 5	100 0	59 3
Timed Vital Capacity 3 sec Per Cent Predicted		79 0	112 1	98 1	58 3	45 9	60	47 7	34	15 6	60 8	8 8	37 6
Maximal Breathing Capacity Per Cent Predicted		98 0	123 0	87 1	60 0	63 6	10 3	89 8	5 9	35 4	73 7	95 7	1 5
Residual Air Per Cent Predicted		65 7	116 0	89 6	112 3	168 8	40 6	68 9	57 1	65 0	1 6 1	13 6	301 9
Total Lung Capacity Per Cent Predicted		80 0	115 5	98 4	72 3	81 7	55 7	50 0	40 7	4 7	74 1	109 8	1 0 7
Residual Per Cent Total Lung Capacity		1 0	5 1	18 2	31 1	48 7	3 3	34 5	8 0	5 6	4 5	36	63.2
Ventilation Factor Per Cent		90 2	111 6	98 3	6 9	53 6	95 8	0 0	60 5	9 7	63 1	87 1	31 6
Arterial Blood Oxygen Saturation Per Cent	Rest Air	89 0	64 8	87 6	85 3	9 7	93 8	1 0	87 8	76 1	93 8	9 5	85
	Rest IPPB Air			87 5	84 5	0 0	96 4		9 0		96 5	93 5	9 0
	Rest 30 Per Cent O									5 8			94
	Rest 40 Per Cent O		89 0	4	86 5								
	Rest 100 Per Cent O	10 6	75 5	97 2	4 4	8 0	9 8	9 0	9	99	6	95 8	7

resting saturation was 93 8% but it was incre[ased] t[o] 96 4% (normal) with intermittent positive pre[ss]ur[e] [b]r[ea]thing on compressed air only thus demonstrating the p[resenc]e of poorly ventilated alveoli The saturation at re[st] [o]n breathing was normal in Case 7 Both patients [s]h[owed] normal saturation (99% or more) on 100% oxygen b[rea]thing at rest However with step up exercise on air breathing they exhibited a marked decrease in arterial blood oxygen saturation

Total lung capacity i[s] often greatly decreased in [s]arc[o]id[o]sis primarily because of a reduction in the vital capacity and commonly the timed vital capacity is the same a[s] the total indicating absence of bronchospasm The re[s]idual air may be reduced in similar proportion to the vital capacity In Case 8 there was a marked reduction in total lung and vital capacities without a significant degree of pulmonary emphysema With intermittent positive pressure breathing on compressed air only significant improvement in saturation at rest was shown indicating the presence of some poorly ventilated alveoli which could be improved On 100% oxygen breathing at rest saturation was normal

In Case 9 the total lung capacity was markedly decreased (24 7% of normal) principally as a result of a marked decrease in vital capacity (15 6% of normal) The residual air measurement was only 65% of the normal predi[c]ted a moderate to marked decrease however with considerable reduction in total vital capacity the residual percentage of total lung capacity is greatly increased This case strikingly demonstrates the importance of comparing both rest and exercise on 100 % oxygen to rule out a shunt conclusively The arterial blood oxygen saturation data indicate that the shunting of blood through nonventilated or poorly ventilated areas is the reason for the unsaturation and not the pre[s]ence of an alveolar capillary membrane block

Asbestosis is frequently accompanied by a significant reduction in total lung capacity a restrictive condition with or without pulmonary emphysema or bronchospasm In Case 10 an asbe[s]tos worker with 37 years exposure had a moderate decrea[s]e in total lung capacity accompanied by a mod[e]rate increase in the absolute value of the residual air and moderate emphysema The exercise arterial bloo[d] oxygen saturation data indicate that the decrease in total lung

gree of unsaturation was very low even on a high oxygen mixture The exercise saturation was even lower both with air and 100% oxygen breathing Ventilation was not a factor as alveolar ventilation was increased and carbon dioxide was blown off at a greater rate than normal as shown by the marked lowering in the arterial co content and P_{CO_2} (by direct tension measurements)

In the presence of multiple small arteriovenous fistulas in all lobes of the lung as in Case 3 the resting saturation on air breathing was considerably higher than that noted in Case 2 The diagnosis in Case 3 was in some doubt only being fully established after death

Shunting of blood from right to left in the heart reveals physiologic findings similar to those in the proved cases of arteriovenous fistulas of the lung In Case 4 with a proved large atrial septal defect and pulmonary hypertension shown by cardiac catheterization saturation at rest was only 86 5% on a 40% oxygen breathing mixture and 94 4% on 100% oxygen With exercise saturation was 54% on air breathing and only 63% on 100% oxygen The small rise in aturation with 100% oxygen in conjunction with the other arterial blood saturation findings indicates that with exercise this patient is able to increase the pulmonary blood flow through the lungs only slightly

Shunting of blood through nonventilated areas in bronchiectasis has shown consistent findings especially with exercise In Case 5 saturation was 91 8% on air breathing and even with a 32% oxygen mixture it was not increased Also intermittent positive pressure breathing on air during step up exercise did not produce any further increase actually saturation was slightly lower than on ambient air breathing These figures indicate that the reduced saturation results from perfusion of blood through nonventilated areas as on 32% oxygen the increased inspired Po was over 70 mm Hg above that on air breathing yet no increase in saturation resulted

In pulmonary fibrosis with slight emphysema the most characteristic findings on the ventilatory side are reduced vital and total lung capacities Fibrosis causes a restrictive condition of the lung with possible absence of bronchospasm Characteristic findings in pulmonary fibrosis of unknown etiology are illustrated in Cases 6 and 7 In the former the

resting saturation was 93.8% but it was increased to 96.4% (normal) with intermittent positive pressure breathing on compressed air only thus demonstrating the presence of poorly ventilated alveoli The saturation at rest on air breathing was normal in Case 7 Both patients had normal saturation (99% or more) on 100% oxygen breathing at rest However with step up exercise on air breathing they exhibited a marked decrease in arterial blood oxygen saturation

Total lung capacity is often greatly decreased in sarcoidosis primarily because of a reduction in the vital capacity and commonly the timed vital capacity is the same as the total indicating absence of bronchospasm The residual air may be reduced in similar proportion to the vital capacity In Case 8 there was a marked reduction in total lung and vital capacities without a significant degree of pulmonary emphysema With intermittent positive pressure breathing on compressed air only significant improvement in saturation at rest was shown indicating the presence of some poorly ventilated alveoli which could be improved On 100% oxygen breathing at rest saturation was normal

In Case 9 the total lung capacity was markedly decreased ([illegible]4.7% of normal) principally as a result of a marked decrease in vital capacity (15.6% of normal) The residual air measurement was only 65% of the normal predicted a moderate to marked decrease however with considerable reduction in total vital capacity the residual percentage of total lung capacity is greatly increased This case strikingly demonstrates the importance of comparing both rest and exercise on 100% oxygen to rule out a shunt conclusively The arterial blood oxygen saturation data indicate that the shunting of blood through nonventilated or poorly ventilated areas is the reason for the unsaturation and not the presence of an alveolar capillary membrane block

Asbestosis is frequently accompanied by a significant reduction in total lung capacity a restrictive condition with or without pulmonary emphysema or bronchospasm In Case 10 an asbestos worker with 37 years exposure had a moderate decrease in total lung capacity accompanied by a moderate increase in the absolute value of the residual air and moderate emphysema The exercise arterial blood oxygen saturation data indicate that the decrease in total lung

suggest that in the past there had been hyperventilation with respiratory alkalosis but with development of severe overwhelming pulmonary edema alveolar ventilation was decreased The increased airway resistance during expiration in patients with pulmonary edema as well as the clinical findings of wheezing and the dramatic response to aminophylline in some patients suggests that bronchospasm is commonly associated with cardiac pulmonary edema

Respiratory alkalosis may be combated by reducing ventilation or by producing metabolic acidosis Ventilation may be reduced by use of morphine and in some instances by inhalation of a high oxygen mixture This type of therapy is most appropriate in acutely dyspneic patients in severe heart failure Ammonium chloride and Diamox* are effective in promoting metabolic acidosis

In emphysema associated with heart failure there is chronic hypoventilation When obstructive emphysema is suspected in a patient with heart disease morphine and oxygen are to be avoided at all costs The depression of respiration caused by these agents may be fatal When it is not clear whether a patient has emphysema with acute pneumonia or bronchitis or whether there is left ventricular failure it is best to use bronchodilators particularly aminophylline until a carbon dioxide content or carbon dioxide tension of arterial blood can be obtained to elucidate whether respiratory acidosis is present

Rapid changes occur in the acid base balance as patients go into and recover from cardiac failure Alveolar ventilation is a quickly changing parameter being followed sluggishly by changes in carbon dioxide content Because the pH is the resultant of the ratio between bicarbonate and carbonic acid it will be changed immediately by variations in ventilation and more slowly compensated by renal mechanisms Thus sudden left ventricular failure undue exertion anxiety or other mechanisms that might produce hyperventilation throw the patient into uncompensated respiratory alkalosis After several hours provided ventilation remains steadily increased compensation of the alkalosis results If ventilation i now suddenly decreased relative to its recent volume respiratory acidosis will occur with low carbon dioxide content

Acute Effects of Breathing Inert Dust Particles and of Carbachol Aerosol on Mechanical Characteristics of Lungs in Man Changes in Response after Inhaling Sympathomimetic Aerosols Arthur B Dubois and Lucien Dautrebande[4] (Univ of Pennsylvania) measured the pulmonary compliance total pulmonary resistance (esophageal pressure method) airway resistance pulmonary tissue resistance thoracic gas volume (plethysmographic methods) and lung volume subdivisions in 5 men without chronic pulmonary disease The measurements were made during a control period before inhalation of small quantities of carbachol micromicellar aerosols and of fine chemically inert dust particles consisting of calcium carbonate powder coal dust activated charcoal powder aluminum powder and aerosolized India ink After inhalation of these aerosols the subjects usually showed definite increase in airway and pulmonary resistance and sometimes slight decrease in lung compliance

Sympathomimetic aerosols were given a few minutes afterward and the same measurements repeated They showed that resistance had fallen below the initial control value and that lung compliance had increased to the normal control value or sometimes beyond the control value

After administration of sympathomimetic aerosols further inhalations of carbachol aerosol or dust particles failed to raise the airway resistance above the initial control value and did not significantly reduce the lung compliance From 15 to 30 minutes after taking 6 25 breaths of carbachol aerosol or dust laden air subdivisions of the lung volume showed no significant change except in 1 of the 5 subjects who had a slight decrease in total lung capacity on the occasion

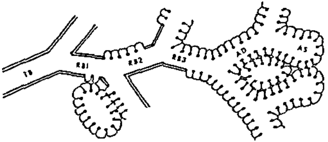
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EMPHYSEMA

Pathogenesis of Pulmonary Emphysema was studied by K H McLean (Univ of Melbourne) The bronchial tree is best regarded as a system of passages dividing dichotomously many times and eventually ending blindly The walls of the proximal passages (the trachea bronchi and bronchioles) are complete The walls of more distal passages (re

(4) J Cl I t 37 1746 1755 Dec mbe 1958
(5) Am J M d 25 62 74 July 1958

spiratory bronchioles alveolar ducts and alveolar sacs) show many small diverticula each a single separate unit the alveolus In the divisions of orders of respiratory bronchioles of which there are usually three progressively more of the wall is represented by interlacing mesh of musculoelastic tissue forming the mouths of the alveoli until in the alveolar ducts nothing remains of the wall other than the open mesh After one further division they terminate in alveolar sacs (Fig 20) Thus in effect each passage is a closed tube the limits of which are alveolar walls Adjacent passages are sep



F g 0—N rmal d ı ı of t rmı al b ch l sh w g th ee d v s of re p t y b h l th mmon t umbe Tw p ag of dj c t a d r l t d ystem h w h w ght g pas ag w th al ol n tl r w ll m y m n cate freely by mean f al eol po *TB* t m n l b ch le *RB1* l t re p t y br ch l *RB2* 2d spı t y b h l *RB3* 3d p rat y b o ch ol *AD* l eol d t d *AS* l la s (Court y of McL an K H Am J Med. 25 6 74 J ly 1958)

arated by two layers of ultrathin alveolar epithelium and a little connective tissue containing capillaries together with elastic tissue and reticulin fibrils These walls are incomplete there being small defects or alveolar pores by which adjacent alveoli and therefore adjacent passages communicate

An important unit of lung tissue is the secondary lobule This is the smallest unit completely enclosed by septa and occupies 1 2 cu mm It is supplied by a bronchiole which after 5 6 divisions ends in a number of terminal bronchioles all situated near the middle of the lobule Their branches supply the rest of the middle of the lobule and the periphery in radial fashion Complete bronchiolar obstruction (especially by mucus) is a common though usually short lived phenomenon even in health

There is close relationship between bronchiolar obstruction and acute bronchiolitis In every respiratory tract infec

tion diffuse and relatively prolonged obstruction and inflammation of the smallest bronchioles occur Such infection is not without sequelae Permanent damage is common and bronchiolar obliteration is not rare It occurs (after obstruction and inflammation) in aerated as well as in nonaerated lung tissue aeration being maintained by collateral ven

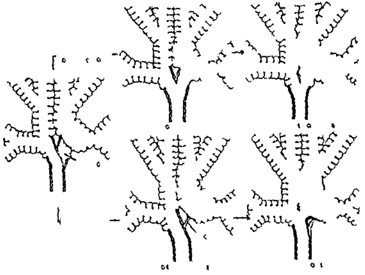


Fig 21 G l (rot) m l d n h poth On l ft dden bl ck f l t l t y b on h l (by pl g hown w h d l t t n d d rupt on t p y b onch i mm d t l d l th Th t mph sem Bl k n b t mp y r m F f nly te p ry be se pl g i xpelled ppe s s) m perma en ha g may sult f rm f perm t d l t t on d som d rupt on f w ll If b h ol bec m bl t t d (l w) t pp g pe (u t l w d conda y comm n cat o a e p od ed C c dentally sc t ff t ted bron h l becom s i p s N t devel pme t f omm n pool n e of d lop g mphy ema nd e se t l m la ty of end re ult w h h p oc l late t g t of en mp actu bl t d t rm n by wh h mech m mph ma d lop d (C rt sy f McLe n K H Am J M d 5 62 74 Jul 1958)

tilation Although collateral ventilation is remarkably efficient with sufficiently extensive obstruction of the bronchioles air trapping may result in the collaterally ventilated lung This may distend and even disrupt passages immediately beyond the obstructed bronchioles (thus producing emphysema) particularly if pressure of the trapped air is considerable as with coughing

Hence primarily emphysema is the result of mechanical forces exerted by air trapped beyond obstructed bronchi

oles duration of the obstruction being one factor determining the degree of change The significance of permanent inflammatory obliteration is obvious the severity of the emphysema being in part proportional to the number of bronchioles obliterated Along with the effect of air trapping in the exudative phase of bronchiolitis alterations in elasticity of the walls of the dilated passages add to the effect produced by the distending force (Fig 21)

► [The significance of pulmonary vascular changes in emphysema has become a subject of increasing interest and discussion The hypothesis has been advanced in recent years that in some forms at least of emphysema the vascular lesions play a primary pathogenetic role In this and in the following article McLean presents the evidence for his view that the vascular changes are nonspecific for emphysema and secondary to pulmonary inflammations which are pathogenetically more important in their effect on the bronchioles Bronchiolar obliteration resulting from inflammation of the smallest bronchioles is in his view the principal cause of emphysema McLean thus differs also with those who regard *partial* obstruction of bronchioles as the most significant pathogenetic factor – Ed]

Significance of Pulmonary Vascular Changes in Emphysema K H McLean[6] (*Univ of Melbourne*) carried out x ray studies on the lungs of 22 patients including 12 with moderate or advanced emphysema In sections from several lungs a recent thrombus was found partially or completely occluding small pulmonary arterial branches This was observed in inflammatory lesions particularly in staphylococcic pneumonias and in noninflammatory pulmonary thrombosis and embolism In instances in which the thrombus did not completely fill the lumen its surface had often been covered by endothelium before the homogeneous eosinophil material representing the clot was changed Phagocytes probably including many of endothelial origin were then noted in the thrombus and at this stage the amorphous material was no longer apparent Gradations were observed between these phagocytic cells and cells of ovoid shape surrounded by intercellular substance

At this later stage the thrombus consisted of a loose network of cells separated by faintly basophil and loosely fibrillary intercellular substance In examples inflammatory in origin the media often showed patchy destruction of muscle and elastic tissue Subsequently inflammatory and noninflammatory lesions showed many thin walled capillaries penetrating the media of the vessel and entering this new tissue It was clear that many completely occluded arteries

(6) A t la n A n M d 69 84 F b y 1958

had been recanalized by proliferating capillaries derived from the vasa vasorum—branches of bronchial arteries—thus forming small interarterial anastomoses The residual tissue within the lumen therefore usually lined the wall but in several examples the lumen of small pulmonary arteries was crossed by an interlacing perforated mesh of tissue indistinguishable from that of thickened intima

There are extensive capillary communications between the bronchial and pulmonary circulations particularly in the region of terminal bronchioles More direct anastomotic channels connecting the two circulations have been described in macroscopically normal lungs both between bronchial arteries and pulmonary veins and between bronchial and pulmonary arteries The interarterial anastomose have been found to increase considerably in many conditions

In the author s specimens the bronchial arteries in macro scopically normal lungs showed gradual tapering of para bronchial branches In such lungs interarterial anastomotic channels were few and small but in all lungs even in the normal the injection material eventually returned through the cut end of the main pulmonary artery and filled the pul monary arterial tree In emphysematous lungs the bronchial arteries were larger and more numerous

Consideration of all the vascular changes found in em physema leads to the conclusion that there is no change specific to the condition Similar vascular lesions are found in all chronic inflammatory lung disease as well as in other conditions These changes in chronic pulmonary inflamma tions are identical in localized and generalized conditions of specific and nonspecific etiology regardless of whether they are manifested primarily by emphysema scarring or bronchiectasis Thus there is no evidence that emphysema results from vascular lesions

Incidence of Emphysema and Its Role in Cardiac and Cir culatory Failure Ludwig Popper reviewed the records of 10 124 patients hospitalized during a 5 year period for one or more of the following conditions cardiovascular disease pulmonary changes (excluding tuberculosis) anemia dis turbed metabolism gastrointe tinal liver and biliary tract diseases genitourinary conditions and rheumatic diseases

Of the study group 2 214 had emphysema mentioned as

(7) W en kl W h h 70 989 99 D 12 1958

Influence of Emphysema on Death Rate in Other Internal Diseases

Diseases		Under 50 Yr			50–59 Yr			60–69 Yr			70 Yr and Over			All Age Brackets		
		T	OD	M	T	OD	M	T	OD	M	T	OD	M	T	OD	M
Hypertension	no E*	44	3	7%	104	5	5%	206	18	9%	116	53	17%	6[illegible]0	[illegible]9	11 7%
	E	6	0	—	56	7	13%	170	26	15%	254	60	24%	396	93	24 1%
Myocardial infarct	no E	24	1	—	93	19	20%	98	36	36%	58	28	32%	303	84	27 7%
	E	1	0	—	24	13	54%	41	22	54%	61	44	72%	127	79	62 3%
Arteriosclerotic heart disease	no E	16	0	—	68	4	6%	121	14	12%	227	49	22%	432	67	15 5%
	E	2	0	—	26	4	16%	36	6	17%	114	41	36%	178	51	29%
Valvular heart disease	no E	126	16	13%	108	26	24%	89	27	30%	64	25	39%	397	94	24 5%
	E	6	3	50%	19	9	47%	29	11	38%	55	36	65%	109	59	54%
Pulmonary infarct, pulmonary embolism	no E	36	4	—	47	3	—	50	11	22%	53	25	47%	196	45	23%
	E	4	3	—	9	5	—	23	17	74%	29	20	69%	65	45	69%
Cerebral accidents	no E	57	18	31%	10	30	26%	205	72	35%	340	154	45%	709	274	38 7%
	E	1	0	—	16	8	50%	55	23	42%	91	45	50%	163	76	47%
Pneumonia	no E	208	2	1%	235	6	2%	143	6	4%	116	16	14%	700	30	4 3%
	E	1	0		19	4	21%	26	5	19%	6	9	25%	82	18	22%
Liver cirrhosis	no E	19	4	21%	114	25	22%	76	20	26%	54	21	39%	263	70	27%
	E	0			5	3		5	4		8	7		18	14	78%

E = emphysema.
T = total number of cases
OD = number of deaths
M = mortality

the main diagnosis only in 547 The incidence of accompanying emphysema varied among the different diseases It was always present in patients of any age group who were hospitalized because of cardiovascular failure This fact underlines the importance of emphysema in development of cardiac failure

The association of emphysema with other diseases generally made the prognosis graver As seen in the table the mortality rate in myocardial infarction was 20% in the age group 50 59 36% at 60-69 and 32% at 70 and over With concomitant emphysema the corresponding incidence figures were 54 54 and 72% respectively Thus emphysema doubles the death rate from myocardial infarcts Similarly emphysema increases the mortality in valvular diseases arteriosclerotic heart disease and hypertension The outlook is gravest in pulmonary infarcts Emphysema seems to precipitate liver failure in cirrhosis

The effect of emphysema depends on the time of its onset the speed of its development and the time when it leads alone or in combination with other diseases to cardiac failure It is striking that the most severe types of emphysema those with the poorest prognosis affect the middle aged more commonly than the old Even in old people emphysema may be of different stages and severity The incidence of emphysema in persons over 50 is estimated as 25 30%

► [This statistical study emphasizes the growing recognition of the enormous prevalence of emphysema and its importance both as a contributory and as a primary cause of mortality It has been stated that in Sheffield England among the laboring section of the population chronic pulmonary disease is a more common cause of heart failure than are coronary disease and hypertension combined (Flint quoted by A V Bates *Recent Trends* i *Chronic Bronchitis* N U Oswald ed) (London Lloyd Luke Ltd 1958) p 172) —Ed]

Regulation of Pulmonary Ventilation in Pulmonary Emphysema Priority of Respiratory Effort over Respiratory Center is discussed by Alvan L. Barach[8] (Columbia Univ) Among the factors which regulate the pulmonary ventilation in patients with pulmonary emphysema the degree of respiratory effort and the associated energy involved in breathing play a significant role Procedures which enhance the efficiency of alveolar ventilation frequently result in a marked lowering of the minute volume of breathing despite the continued presence of hypercapnia

(8) A M A A h I t M d 103 914 J nua y 1 59

A decreased pulmonary ventilation has the special advantage in the emphysematous subject of markedly decreasing the amount of carbon dioxide produced Since hyperventilation of 15 L/minute may require the same amount of respiratory work that a normal person performs breathing at more than double that volume the initiation of a lower ventilation as a result of more efficient aeration of better parts of the lungs is followed by a beneficial cycle of lower carbon dioxide production and hence a diminished ventilatory requirement

The response of the patient with pulmonary emphysema to a regulated oxygen program is characterized by a decrease in the volume of breathing the resultant increase in arterial carbon dioxide tension is not considered a manifestation of insensitivity of the respiratory center to carbon dioxide but rather an indication of a priority of the mechanism that leads to reduction in the work of breathing and consequently dyspnea This mechanism includes the sensitivity of the carotid sinus to arterial hypoxia adaptive compensatory elimination of carbon dioxide at high partial pressures in the alveolar air and a decrease in oxygen requirement and carbon dioxide production

It has been shown that patients with pulmonary emphysema respond to inhalation of carbon dioxide in a manner similar to normal persons who have imposed on them a comparable restriction in maximal breathing capacity the concept of insensitivity of the respiratory center to carbon dioxide as a result of hypercapnia is questionable and therefore the therapeutic proposals to blow off carbon dioxide routinely by hyperventilation devices The homeostatic equilibrium of these patients may indeed be altered but the clinically well adapted patient (i e without uncompensated acidosis) is not benefited by artificial reduction in Pco and bicarbonate

Substitution of diaphragmatic for thoracic respiration is accompanied by a sharp reduction in ventilatory effort and in the volume of breathing without reduction in hypercapnia or hypoxia The priority of factors which decrease the work of breathing over chemical stimuli to the respiratory center and to the carotid sinus was also demonstrated in patients in whom reserve volume respiration was increased by a pneumatic breathing aid

► [Barach here presents in a carefully reasoned and admirably concise manner the principles underlying his program of treatment in emphysema In emphasizing the advantage of a d cr ased pulmonary ventilation pro du ed by a regulated oxygen program *ad n nistered without hyperventila tion d-ces* he differs with those who regard the blowing off of carbon dioxide as the prime desideratum in all patients with carbon dioxide re tent on even tho e without uncompensated acidosis Barach s concept of the homeostatic nature of the response of the patient with pulmonary em physema to oxygen inhalation is supported he b lieves by recent studi s on the work of breathing His thesis that the regulation of the pulmonary ventilation in emphysema is governed more by factors responsible for re piratory effort than by impaired sensitivity of the respiratory center resulting from hypercapnia appears to be substantiated at least in part by the findings of Richards Fritts and Davis (p 117) —Ed]

Treatment of Pulmonary Insufficiency by Tracheal Fenestration Preliminary Report is presented by Edgar Mayer Charles F Blazsik and Israel Rappaport[9] (New York) As pulmonary reserve diminishes patients become increasingly sensitive to the least interference with the patency and free flow of air in the airways of the lungs With progression of pulmonary insufficiency the need arises for an early and permanent tracheal opening to permit intubation and aspir ation of the deeper airways as often as necessary Tracheal fenestration provides such an opening which can be opened and closed at will It offers an effective method for relieving hypoventilation crises and it appears to be the best proce dure for preventing such crises in progressive pulmonary in sufficiency It is also of great advantage in inhalation therapy

Tracheal fenestration was performed on 6 patients who were approaching terminal hypoxia as a result of destructive pulmonary disease It was then possible to remove muco pulmonary secretions by aspiration a procedure which the patient gradually learns to do for himself The immediate re lief after aspiration and the striking change for the better in the course of the disease indicate that the advantages of tracheal fenestration need to be further explored

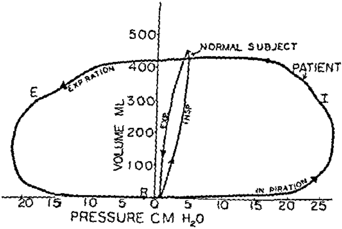
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ASTHMA

Mechanics of Respiration in Bronchial Asthma were studied by Roe E Wells Jr[1] (Harvard Med School) in 10 patients with long standing disease during periods of acute respiratory distress and after relief from or improvement of

(9) J A.M A 167 696 701 J 7 1958
(1) A J M d 26 384 393 M h 1959

symptoms as a result of therapy Work of breathing was calculated from pressure volume loops plotted from the simultaneous pressure volume recordings of 3 6 representative breaths By planimetric integration of these loops an approximation of average work done on the lungs could be determined Because the work of breathing in these patients involved active work during expiration integration of these loops included the area circumscribed by the expiratory pressure volume tracing beyond the resting end expira-



F g 22 C mp n f p u lu loop f p t nt d m l l; ! W k f br th g f p t t a f l g loop RIER R p nt pat ts t g end xp x y) (C u i y f W ll R E J Am J M d 6 384 393 M r h 1959)

tory pressure as well as the area under the curves produced by elastic and inspiratory flow resistive work Figure 22 describes the work loop of 1 subject with extremely high flow resistance The width or fatness of this loop is compared to that of a normal subject

Mean airway resistance was markedly elevated in all the patients Analysis of the individual inspiratory and expiratory airway resistances indicated that inspiratory airway resistance may be almost as high as expiratory resistance After therapy most patients showed greater improvement in inspiratory resistance than in expiratory resistance Thus the prevailing impression that most if not all the obstruction to air flow in bronchial asthma is always in the expiratory pha e cannot be supported

Based on the relatively equal values of expiratory and inspiratory flow resistance found in 5 of 10 patients it is possible that the check valve mechanism is not always operative in all patients Elastic resistance of the lungs expressed as compliance appears to decrease as nonelastic (airway) resistance increases

The work of breathing in patients during attacks of bronchial asthma is markedly increased and is due almost entirely to the work done in overcoming airway resistance Any therapeutic procedure directed toward lowering the elevated airway resistance is therefore rational and justified on the physiologic basis of its effectiveness in diminishing the work of breathing

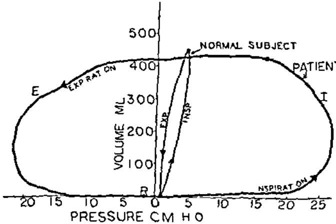
Long Term ACTH and Corticosteroid Therapy in Bronchial Asthma Clinical Evaluation Hans Arnoldsson[2] (Goteborg) treated 106 women and 55 men with average age of 54 and mean duration of disease of 15 years who had endogenous bronchial asthma of such severity and intractability that corticoid therapy was considered essential The patients first received a preliminary course of ACTH or corticosteroids combined with bronchodilators and expectorants Response was excellent in 65 2% good in 25 5% and poor in 9 3% Those born in even years were continued on ACTH or corticosteroids as were 10 born in odd years the others were given symptomatic therapy or placebo The treated group and the control group thus were essentially similar Altogether 63 transfers to the treated group were made Of the ultimate treated group of 144 patients 70 were treated with 5 mg prednisone daily and 46 with 10 mg The others received ACTH or corticosteroids singly or in combination

After average follow up of 25 months 37 5% of the patients were free from asthma 42 3% had mild symptoms occasionally and 20 2% had moderate to severe asthma Incidence of untoward reactions was objectively insignificant and included cardiac and circulatory disturbances aberrations of water and electrolyte metabolism neurologic and psychiatric manifestations gastroduodenal (peptic) ulcer allergic reactions to ACTH osteoporosis and adrenocortical hypofunction

No patient had clinical signs of peptic ulcer at the begin

(2) \ ]] ≠ 1 1 1 pp 6 1938

symptoms as a result of therapy Work of breathing was calculated from pressure volume loops plotted from the simultaneous pressure volume recordings of 3 6 representative breaths By planimetric integration of these loops an approximation of average work done on the lungs could be determined Because the work of breathing in these patients involved active work during expiration integration of these loops included the area circumscribed by the expiratory pressure volume tracing beyond the resting end expira



Fg 2 Cmp n f p u v l m l p f p t ent a d n mal bject. Wo k f b th g f jat t a de la g loop *RIFR R* p t p t t r t ng l p y f (C urt y f W ll R E J Am J Med 6 384 393 M h 19 9)

tory pre ure a well as the area under the curves produced by elastic and inspiratory flow resistive work Figure 22 describes the work loop of 1 subject with extremely high flow resistance The width or fatness of this loop is compared to that of a normal subject

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in 2-4 minutes There was no contraction of the bronchiole which was then lightly swabbed and 0 01% epinephrine was applied Again there was no detectable change in total thickness but the lumen widened within 10 seconds Atropine and papaverine when applied instead of epinephrine produced no change

The hilar structures were exposed routinely at operation and after removal of the affected segments the right vagus nerve was infiltrated with Xylocaine* from the level of the 1st dorsal vertebra to the hilus The stellate ganglion and dorsal ganglions of the sympathetic chain were also infiltrated as far as the level of the 7th dorsal vertebra A ring of edema was raised in the alveolar tissue around the main bronchus main pulmonary artery and the upper and lower veins

No alteration in the caliber of bronchioles on the raw intersegmental surface was observed when vagus and sympathetic nerves were blocked separately and together Immediate postoperative bronchoscopy after thoracotomy closure (the ipsilateral pupil still showing dilation) revealed no alteration of rhythmic bronchial respiratory variation as compared with the other side of the bronchial tree

► [The lack of evidence of myohypertrophy in the bronchioles of patients with histories of asthma as well as direct observations of bronchiolar respiratory movements and their lack of response to humoral and neural effects forms the basis of the author s conclusion that muscular constriction of bronchi bears little relation to the pathogenesis of clinical bronchospasm It is among thoracic surgeons particularly that one most often hears scepticism concerning the importance or even existence of true bronchospasm Certainly a reappraisal of this established concept is in order Wells (p 141) though he does not reject the concept of the constriction of bronchial musculature at least as the initial event of an asthmatic paroxysm also emphasizes the importance of edema and of blockage of the bronchial lumen by secretion in the continuance of the attack —Ed]

ning of therapy During treatment 21 (14 6%) of the patient were diagnosed as having altogether 32 peptic ulcers Five duodenal ulcers and 1 gastric were reactivations of prior ul cers These figures are at least 10 times as high as the normal new ulcer expectation rate

Allergic reactions to ACTH were observed in 8 patients X ray signs of osteoporosis were found in 28 (19 7%) pa tients 27 were women and 25 of these were postmenopausal In 82 asthmatic controls of similar sex and age distribution x ray evidence of osteoporosis was found in 9 (11%) over age 57 7 of whom were women The preponderance of x ray osteoporosis in the treated group combined with the fact that 3 patients had spontaneous vertebral compression frac tures and 2 had pelvic fractures after slight trauma suggests that the osteoporosis was in part steroid induced Consider ing that 89% of the patients with osteoporosis were postmen opausal women adjuvant treatment with combined andro gens and estrogens seems advisable for such patients on long term ACTH or corticosteroid therapy

Clinical Studies on Bronchospasm R R. Gilfillan[3] stud ied 6 men and 6 women aged 22 27 during segmental lung resection which was performed for segmental tuberculous lesions Six of the patients had a history of bronchospastic attacks The mechanism of bronchiolar respiratory move ment was studied directly at operation with a hand lens Healthy bronchioles of 0 5 mm diameter ruptured across the intersegmental plane during stripping of the segment and other bronchioles which had been stripped along their length showed rhythmic variation in caliber with pressure changes in the anesthetic apparatus The effect of temporary occlusion of the feeder bronchus was then observed The subsegmental bronchus to the area in which lay the bron chioles under study was occluded by a rubber shod clamp Respiratory excursions persisted although more slowly due to air drift from adjacent unoccluded segments which filled the alveoli around the bronchioles and distracted their walls circumferentially

A few bronchioles were studied histologically There was no evidence of myohypertrophy in asthmatics as compared with normal persons When a few minims of 50% histamine was dropped on the open bronchiole the lumen diminished

(3) J Th r Su g 36 63 69 Jul 1958

in 2-4 minutes There was no contraction of the bronchiole which was then lightly swabbed and 0 01% epinephrine was applied Again there was no detectable change in total thickness but the lumen widened within 10 seconds Atropine and papaverine when applied instead of epinephrine produced no change

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Peripheral Pattern in Normal Bronchogram and Its Relation to Peripheral Pulmonary Anatomy was studied by Lynne Reid and G Simon[4] (London) Along the distal 10 cm of an axial bronchial pathway, two patterns of branching can be distinguished (Fig 23) the centimeter and millimeter

In bronchograms there may be so much radiopaque material in the lungs that it causes a more or less confluent

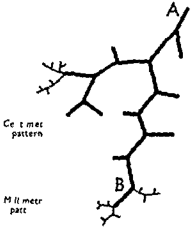


Fig 23 —Tatt r f b h g f nd f b onchial p thway At f st b an h r e at terv l f bo t 0 5 1 m (A t B) beyond B they a ise at te als ot abo t mm (about t ral t) (Cou te y of R d L a d Simo G Tho x 13 103 109 June 1958)

woolly shadow By comparing bronchograms taken at different angles it is often possible to show that such appearance results from superimposition of line shadows Sometimes a punctate shadow may be observed overlying a line shadow directly (Fig 24) or slightly to one side This may give a somewhat bulbous appearance to the parent line Figure 24 also shows several punctate shadows which in lateral view were established as side branches viewed end on Such shadows are no wider than the line with which they are as

(4) Thorax 13 103 109 J e 1958



Fg 24 P n t te h d w ly g l pp rro) Ri g had w (ou w) lso lt d f m j po t n f } r d ed f m 1 5 (Court y f R 1 L d S m L Th a 13 103 109 J n 1958)

sociated A ring shadow of somewhat greater diameter than that of a bronchiole (3 5 mm) is sometimes seen where there is intensive peripheral filling

Correlation with the histology hows that the centimeter pattern mostly represents bronchi but a varying number of its peripheral branches represents bronchioles whereas the more closely set millime er pattern represents terminal bronchioles

Bronchiolectasis in Chronic Bronchitis is characterized by saccular dilatation of the terminal bronchioles The more proximal bronchi may or may not show radiologic changes

Carl F Wisoff (Norfolk Va Gen l Hosp) studied 2 men aged 39 and 49 with bronchiolectasis Both complained of chronic cough and chest pain In both the lungs appeared normal by fluoroscopy and on chest films Bronchograms showed peripheral pooling of contrast material in the termi

(5) R 1 1 gy 70 848 850 J 1958

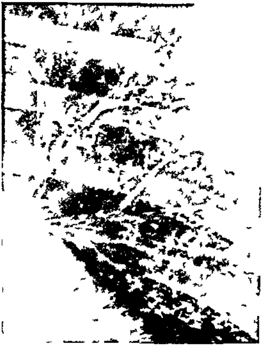


Fig 25—Left upper lobe showing bronchiolectasis ... 39
(Courtesy of W soff C P Radiology 70 848 850 June 1958)

nal bronchioles involving most of the segments (Fig 25)

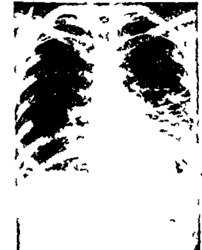
Reports of bronchiolectasis in the literature are too sketchy to determine its incidence in bronchiolitis or chronic bronchitis and emphysema or the relation of this finding to the clinical symptomatology The pathologic findings which in some cases have shown no chronic fibrotic changes suggest that peripheral pooling may sometimes be reversible

Bronchiectasis in the Maori was studied by J R Hinds[6] (Green Lane Hosp Auckland) in 65 patients Severity of the disease was estimated on an anatomic basis as shown by the extent of lung involvement at bronchography The degree of severity was based on the number of lobes involved Incidence of extensive disease was considerably higher among the Maori than among controls made up of Europeans with bronchiectasis The saccular and cystic (Figs 26 and 27) forms of bronchiectasis were much more common among the

(6) New Zealand M J 57 3 8 332 August 1958

Maoris Incidence in the groups aged 0 10 11 20 and 41 50 was similar among Europeans and Maoris In the group aged 21 30 incidence among the Maoris was 2½ times that among the Europeans In the group aged 31 40 incidence among the Europeans was half as high as among the Maoris and in the group aged over 50 incidence among the Europeans was four times higher than among the Maoris

Existence of a congenital basis to explain some forms of bronchiectasis has never been satisfactorily established no





Fg 26 (l ft) —Cy t d se e h d to l ft upp l be (s p b bbl) m M g l 16
Fg 27 (ight) —L n t n t m m p t t (C t y f H l J R N w Z l nd M J 57 328 33 A g t 1958)

extrapulmonary evidence of associated congenital defects was observed in any of these saccular cystic forms of the disease There was no example even of dextrocardia associated with bronchiectasis (Kartagener s syndrome) nor evidence to suggest that these patients were afflicted with fibrocystic disease of the pancreas Examples of cystic disease may be residues of some acute pneumonic process The author saw bullous cysts associated with healing of staphylococcic lung infections in infants and children as a prominent striking feature What ultimately becomes of some of these lesions is not known and although complete resolution is

known to occur a few may carry over to adolescence or adult life as persistent cysts These 'soap bubbles are not simple emphysematous bullae or pneumatoceles but are lined throughout with normal ciliated columnar epithelium Possibly the cavities resulting from bronchial wall destruction are relined respiratory epithelium growing from neighboring healthy bronchi

Long Term Treatment of Bronchiectasis and Chronic Bronchitis Controlled Study of Effects of Tetracycline Penicillin and Oleandomycin Penicillin Mixture Neil S Chermack Kenneth L Vosti Harry F Dowling Mark H Lepper and George Gee Jackson[7] (Univ of Illinois) treated 67 patients with chronic bronchitis or bronchiectasis in a double blind study for 3 22 months Group 1 received 2 Gm tetracycline daily in four divided doses one half hour before each meal and at bedtime Group 2 received 1 Gm potassium penicillin G (1 600 000 units) daily in four divided doses group 3 received daily 2 Gm of a combination 1 3 Gm oleandomycin penicillin and 0 7 Gm penicillin in four divided doses Group 4 received a sucrose placebo 4 times a day All medications were dispensed in capsules of identical shape size and color

Patients who received tetracycline had significantly fewer lower respiratory illnesses febrile or afebrile than those treated with placebos The average duration of these illnesses was shorter in patients treated with tetracycline They also had significantly fewer days of respiratory illness with or without fever than patients treated with penicillin alone Patients treated with combined oleandomycin and penicillin had significantly fewer days of lower respiratory illness than those treated with placebo and also fewer days of illness with fever than those receiving penicillin alone Therapy with penicillin alone was no more effective than placebo therapy There was no significant reduction in sputum volume or purulence and no significant gain in weight or improvement in pulmonary function in patients on antibiotic therapy

Tetracycline significantly reduced the frequency of isolation of Diplococcus pneumoniae (pneumococci) and coagulase positive staphylococci from these patients Frequency of isolation of Hemophilus influenzae was also reduced but not significantly Oleandomycin penicillin combined reduced the

(7) A M A A h Int Med 103 345 353 M b 1959

frequency at which coagulase positive staphylococci were isolated Patients from whom H influenzae was isolated had more days of lower respiratory infection than did those from whom this micro organism had never been isolated In all groups C reactive protein decreased insignificantly Pulmonary function was not appreciably altered during the 1st year of therapy

PNEUMOCONIOSIS AND OTHER INHALATION DISEASES

Rheumatoid Pneumoconiosis in Foundry Worker A Caplan E D H Cowen and J Gough[8] point out that the chest x rays of workers exposed to various dust hazards including coal present a particular radiographic appearance which is similar to that seen in rheumatoid disease The characteristic x ray features are multiple well defined round opacities 0 5 5 cm in diameter distributed throughout both lung fields In many patients the background of simple pneumoconiosis is slight or absent and the opacities often appear with a suddenness that is not usual in the development of ordinary progressive massive fibrosis The opacities may appear before coincidentally with or after onset of arthritis and there is no apparent relation between the severity of the arthritis and the extent and type of the x ray changes In some the opacities increase in size and number and crops of fresh lesions may appear every few months whereas in others only a few round opacities are localized to one or more areas of the lung fields and remain stationary The lesions may cavitate and disappear or fibrose Calcification is fairly common and in many instances the lesions ultimately become incorporated in progressive massive fibrosis Usually the x ray picture shows a mixture of round opacities progressive massive fibrosis and opacities indistinguishable from tuberculous lesions (Fig 28) Macroscopically the lesions show a characteristic concentric arrangement of lighter and darker layers The pale areas sometimes are gray and sometimes yellow Liquefaction tends to occur in the pale areas leaving clefts Sometimes the nodules are densely calcified

(8) Thorax 13 181 184 Sept mber 1958

The histologic criteria are a central area of necrotic collagen outside of which is a zone of active inflammation consisting of a cellular infiltration of macrophages and often also of polymorphonuclear leukocytes In this zone collagen is being destroyed In hematoxylin eosin stained sections the intense blue staining of the inflammatory zone contrasts with the pink of the central necrotic collagen Some macrophages in the inflammatory zone contain dust When these



F g 28 —Ro d p t w d sp d th gh t all f b th l g fi ld w th oal e f p t pp m d d l w r (C urte y f C pl A *et l* Th ax 13 181 184 S pt mb 1958)

macrophages die and disintegrate the dust is deposited Thi accounts for the dark concentric rings seen in the nodules The inflammatory zone may involve all or only part of the circumference of a nodule Multinucleated giant cells are present in some instance These lie in a zone of fibroblasts outside the zone of inflammatory cells The fibroblasts are orientated in a palisade manner Outside the palisade is a zone of collagen arranged circumferentially and not necrotic Endarteritis is present in vessels at the periphery of the nodules and in the lumen of the vessels there are more

lymphocyte and plasma cell than seen in the endarteritis usually present in pneumoconiosis

► [This condition of rheumatoid pneumoconiosis originally described in 1953 by Caplan in coal workers and known to others as Caplan s syndrome has since been described in workers exposed to other dusts as in the present case report The association of arthritis with pneumoconiosis presenting a particular radiographic appearance has thus been noted not only in coal workers pneumoconiosis but also in silicosis arising in various industries involving silica hazards and in 1 case of asbestosis Gough previously made detailed pathologic studies of the lung lesions in 16 instances of the syndrome in coal workers and reported characteristics which distinguish these lesions from the progressive massive fibrosis of this pneumoconiosis (regarded more widely in Britain than in the United States as a condition different from silicosis) as well as from the classic silicotic nodule It is surprising therefore that this characteristic process should occur in such a variety of pneumoconioses of different etiologies (coal workers pneumoconiosis silicosis and asbestosis) The following paper is the first report of a case of Caplan s syndrome in the American literature —Ed]

Caplan s Syndrome Perplexing Pneumoconiosis with Rheumatoid Arthritis Milton Kantor and Charles S Morrow[9] (V A Hosp Wilkes Barre Pa) call attention to the development of pulmonary changes during the course of various types of so called collagen diseases including rheumatoid arthritis These rheumatoid pulmonary lesions do not present a characteristic roentgen appearance in the absence of pneumoconiosis but in the presence of such a dust disease they may do so Multiple well defined round opacities in the lungs of patients with pneumoconiosis have been described by Caplan as frequently associated with rheumatoid arthritis However the Caplan type of pulmonary lesion may appear without rheumatoid arthritis

The authors report a case of Caplan s syndrome in a man 64 which differed in several respects from that originally described by Caplan Many of the pulmonary opacities developed from the conglomerate lesions of 3d stage anthracosilicosis Two of these opacities were larger than 5 cm and calcific aortic stenosis which may be etiologically related to rheumatoid arthritis was found

The authors case was the only one among 150 patients with anthracosilicosis of whom 15 had associated rheumatoid arthritis and 35 had complicating silicotuberculosis

Farmer s Lung Acute Granulomatous Interstitial Pneumonitis Occurring in Agricultural Workers Helen A Dickie and John Rankin[1] (Univ of Wisconsin) describe this as a

(9) Am Rev Tuberc 78 274-283 August 1958
(1) J A M A 167 1069 1076 July 28 1958

potentially serious and crippling disease that results from handling various dusty moldy organic materials The symptoms are shortness of breath cough fever, chills weight loss and hemoptysis This condition differs from silo filler s disease in causation and symptoms X ray findings are tho e of



Fg 29—Lu g t f mm 2 l w g h ct t g ulmtu t tt l t du d f 150 (C rt y f D k H \ d R k J J A M A 167 1069 10 (J 8 1958)

interstitial pneumonitis Lung biopsy reveals a granulomatous interstitial pneumonitis with epithelioid and giant cells

Of 39 patients observed with this syndrome lung biopsy was done in 8 Six of the specimens revealed a granulomatous interstitial pneumonitis with epithelioid and giant cells (Fig 29) Repeated exposure was followed by recurrence No causative organism was found A given exposure induced the disease in some persons but others were unaffected Treatment is preventive avoidance of exposure

Bagassosis Review with Further Historic Data Studies of Pulmonary Function and Results of Adrenal Steroid Therapy is presented by Howard A Buechner Amos L Prevatt Jordan Thompson and Oscar Blitz (Tulane Univ) Bagasse

(2) Am J M d 25 234 247 A g t 1958

is the fibrous material remaining after the sugar containing juice has been expressed from sugar cane It is either dis carded burned or used in the manufacture of insulating and acoustic materials paper fertilizer explosives poultry feed and refractory brick

Bagassosis or bagasse disease of the lungs is a disorder resulting from the inhalation of bagasse dust It is typically an acute pneumonitis or bronchiolitis often associated with x ray features resembling miliary tuberculosis Dyspnea is the most characteristic symptom although cough hemopty sis fever weakness and weight loss are often present Com plete recovery usually occurs after a few weeks or months However shortness of breath may persist for months or even years after all other signs of the illness have disap peared

Pulmonary function studies in 2 patients indicated alveo lar hypoventilation secondary to bronchiolitis When the ill ness is pronounced symptomatic therapy is beneficial How ever when symptoms are particularly severe and progressive even oxygen and intermittent positive pressure breathing will not completely relieve the air hunger In 2 such patients adrenal steroids had a beneficial effect

Beryllium Disease is discussed by Harriet L Hardy and John D Stoeckle[3] (Massachusetts Gen l Hosp) Until re cently extraction of beryllium from the ore beryl and the manufacture of fluorescent lighting were considered the chief sources of beryllium poisoning The list of sources has lengthened to include the industries and industrial op erations listed in Table 1

A few patients with acute beryllium poisoning apparently recover but later become the victims of the chronic form In most patients however the disease develops without an acute stage several weeks to years after their last exposure to beryllium Table 2 summarizes the latent period between the last exposure and onset of symptoms

The most common symptoms in the chronic form are dysp nea on exertion and cough usually nonproductive Weight loss with or without anorexia weakness and fatigue are prominent Chest pain is noted in nearly one third of the pa tients This pain may be typically pleuritic or may be the muscular discomfort of labored respiration A few patients

(3) J Chron. D 9 152 160 F bru ry 1959

have unexplained febrile episodes The major complications in the chronic disease are spontaneous pneumothorax (12%) and renal stones (10%) Tuberculosis is striking by its near absence

Chest x rays show diffuse pulmonary involvement with discrete miliary nodular densities Hilar adenopathy may be present The picture is not specific and must be differentiated

TABLE 1 —INCRIMINATED BERYLLIUM USING-OPERATIONS

Extraction of beryllium	Beryllium metallurgy
Fluorescent 1owd r manufacturing	Ceramic operations
Fluorescent lamp manufacturing	Radio tube manufacturing
Fluorescent lamp salvage	Atomic energy development
Neon sign manufacturing	Neighborhood contamination
Beryllium alloy manufacturing	Use of alloys containing more than 4% beryllium

TABLE 2 —TIME FROM LAST EXPOSURE TO FIRST SYMPTOMS

	No of C	%
Less than 1 mo	126	41
1 mo to 1 yr	27	9
1 5 yr	89	29
5 10 yr	56	18
More than 10 yr	12	4
Total	310	101

Maximum 15 yr

from other granulomatous diseases I aboratory findings have shown alteration in the serum proteins with elevation of globulins

At high doses of exposure to harmful beryllium compounds a specific fibrinoid pneumonitis with considerable edema has been seen in the few cases in which autopsy has been done Toxic beryllium compounds when inhaled in harmful quantity produce in the chronic form an inflammatory response difficult to distinguish from the changes seen in Boeck s sarcoid The characteristic lesion reported is a noncaseating granuloma in which beryllium may be demonstrated In addition there is considerable round cell infiltration as part of the inflammatory response Although the lung is most frequently involved liver spleen kidney hilar and abdominal nodes heart muscle and striated muscle may also be affected

Steroids in adequate doses influence favorably the clinical

course of chronic beryllium disease Skin lesions spleen enlargement and such abnormalities as hypercalciuria disappear The most important consistent finding is that the oxygen unsaturation caused by the marked changes in beryllium poisoning is reversed to a remarkable extent accounting for the clinical improvement

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TUBERCULOSIS

Community Trials of BCG Vaccination Carroll E Palmer Lawrence W Shaw and George W Comstock[4] (USPHS) present a progress report on two controlled trials of BCG vaccination after a follow up of 6-7 years One trial on children aged 1 18 years was conducted in Puerto Rico and the other on persons over age 5 in Muscogee County Ga and Russell County Ala More than 250 000 persons were placed under study 112 000 tuberculin reactors and 144 000 nonreactors who were allocated at random into vaccinated and control (unvaccinated) groups

The most striking feature of both trials was that the risk of contracting tuberculosis was much greater for persons who were tuberculin reactors on entry than for those who were nonreactors Of the total number of cases that appeared during the follow up period 75% were in reactors consequently only the 25% that would have appeared among the initial nonreactors could have been prevented if vaccination had been completely effective

Tuberculosis case rates among nonreactors were low (Table 1) In Puerto Rico the rate was 43/100 000 initial population/year among controls and 30 among vaccinees The 31% fewer cases among the vaccinees is statistically significant (Table 2) In the Muscogee Russell trial the corresponding rates were 22 among controls and 14 among vaccinees but the difference (36%) is not statistically significant If all nonreactors had been vaccinated the total number of cases in the study populations would have been reduced by 8-9%—an estimate obtained by applying a reduction of 31 36% to the 25% of cases which would have appeared in those who could have been vaccinated

(4) Am Rev Tuberc 77 877 907 Jun 1958

TABLE 1—INCIDENCE OF TUBERCULOSIS AMONG REACTORS AND NONREACTORS*

Tuberculin Sensitivity	Study Population	Number of Cases	Average Annual Incidence per 100,000	
			Crude	Adjusted†
Puerto Rican Trial				
Total	191 8[illegible]	1 149	95 3	—
Reactors	8[illegible] [illegible]69	8[illegible]6	103 3	165 8
Nonreactors	109 5[illegible]8	[illegible]03	43 1	40 9
	Ratio of rates		3 8	3 5
Muscogee-Russell Trial				
Total	64 136	216	48 2	
Reactors	[illegible] 361	161	8[illegible] 3	67 1
Nonreactors	34 [illegible]67	[illegible]	2[illegible] 4	31 6
	Ratio of rates		3 5	2 1

*With effect of vaccination removed
†Adjusted to the age composition of the total study population of each trial

TABLE 2—INCIDENCE OF TUBERCULOSIS AMONG CONTROLS AND VACCINEES

Trial and Category	Study Population	Number of Cases	Average Annual Incidence per 100,000
Puerto Rican Trial			
Controls	2[illegible] 338	3[illegible]	43
Vaccinees	[illegible]0 634	[illegible]3	[illegible] 8
Reduction in tuberculosis morbidity among vaccinees —30 9			
Muscogee-Russell Trial			
Controls	17 854	8	[illegible] 4
Vaccinees	16 913	17	14 4
Reduction in tuberculosis morbidity among vaccinees —35 9			

The low case rates among nonreactors can be directly attributed to the present low risk of acquiring new infections. Since BCG cannot help those who are infected or who will not become infected and may be helpful only to a portion of the decreasing few who will acquire infection, it is apparent that vaccination cannot be of great value in controlling tuberculosis in this country. Moreover, with the rapid decline

in tuberculous infection the tuberculin test is becoming increasingly more valuable for epidemiologic case finding and diagnostic purposes The advantages of the tuberculin test are destroyed by vaccination which makes identification of naturally infected persons virtually impossible The position is taken that in view of the present situation in this country the advantages of vaccination are outweighed by the disadvantages

► [These conclusions of Palmer and his associates will displease those who have called for a more extensive use of BCG vaccination in the United States Even the limited recommendations made recently by two advisory committees (1958 59 YEAR BOOK pp 169 and 170) that the vaccine be given to certain special groups receives less than enthusiastic endorsement here The authors point is well taken that the risk among such groups as nurses medical students hospital attendants and labora workers is by no means uniform and that even among these traditionally high risk groups a BCG program is not desirable in all instances —Ed]

Remarks on the clinical management of tuberculosis by William B Tucker[3] (VA Washington D C) based on his participation in the cooperative studies of the Veterans Ad ministration and Armed Forces deal with concrete ques tions for example whether there is a single drug of choice At present there is little debate but that isoniazid is the most effective single drug in tuberculosis Large series of cases have indicated that *in general multiple therapy is de irable* to prevent drug resistance and loss of susceptibility But these observations do not necessarily apply to all subgroups such as those of minimal and moderately advanced (particu larly noncavernous) disease in which isoniazid alone has been effective For minimal tuberculous conditions it may be appropriate to change after an initial period of 2 drug ther apy to isoniazid alone

In cavernous pulmonary tuberculosis especially when cav ities measure over 2 cm in diameter 2 drug combinations such as isoniazid streptomycin or isoniazid PAS are sug gested The objection to the use of both isoniazid and strep tomycin on the theory that the 2 best drugs would no longer be in reserve if there is therapeutic failure is not to be taken too seriously since the combination is highly effective Fur ther there are several second line drugs available

Since intermittent streptomycin is less effective than daily streptomycin as a *companion to daily isoniazid in more ad*

(3) Am R T be 8 333 345 S ptem I 1959

vanced cases it is wise to recommend the drug on a daily basis at least for the first 2 months of treatment or until cavities close, sputum converts or the disease otherwise approaches reasonable stability. After this streptomycin may be given intermittently. Daily administration is widely accepted by most patients, including the elderly, if there is proper orientation.

The combination of PAS with isoniazid has been found to be practically equivalent to isoniazid and streptomycin daily

GENERAL REGIMENS AND RESULTING TOXICITY

	Regimen					
	Isoniazid + PAS		Isoniazid + Streptomycin		Isoniazid + Streptomycin + PAS	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
Number of patients	197		193		237	
Incidence of toxicity	20	11	43	22	9	41
To isoniazid	1	1	3	2	5	2
To streptomycin	—	—	40	20	54	23
To PAS	19	10	—	—	39	16
Toxicity causing change of drugs	12	7	29	15	51	22
To isoniazid	1	1	3	2	2	1
To streptomycin	—	—	26	13	32	14
To PAS	11	6	—	—	17	7

and more effective than isoniazid daily and streptomycin intermittently.

Comparison of 3 drug with 2 drug therapy as regards x-ray improvement and conversion of sputum or gastric contents by culture has revealed no superiority of the former over either 2 drug regimen, even in far advanced disease. For a few patients all 3 drugs may actually be indicated. Their routine use, however, is not justified. As the table indicates, the incidence of toxicity was greater when all 3 drugs were used.

A few patients will need more than 5 mg. isoniazid/kg. body weight because their metabolic inactivation of isoniazid is so rapid that ineffective concentrations in plasma and presumably in various body tissues result.

Duration of drug therapy is another variable in treatment of which there has been *no satisfactory subjective study* to date. Examination of data from the cooperative studies during 1950–52 when streptomycin and PAS were used for vary

ing lengths of time (Fig 30) suggests that somewhere be tween 18 and 24 months the asymptote may be reached or nearly reached It is probable that with sufficient data different optimum durations could be established for differ ent degrees of disease These might range from about 8 months for the most minimal minimal to possibly truly indefinite duration for the most advanced cases

Besides the 3 drugs most commonly used there are at least 10 new separate and distinct drugs of varying effectiveness

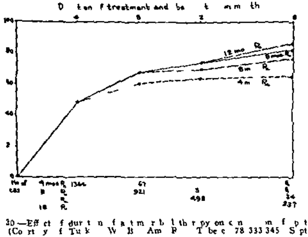


Fig 30—Effect of duration of antimicrobial therapy on ... by culture (Courtesy of Tucker W B Am Rev Tuberc 78 333 345 September 1958)

toxicity and usefulness On the basis of mathematical calcu lation these would provide 45 possible 2 drug combinations many of which have actually been used and reported on

Current studies in steroid therapy demonstrate that ste roids may be life saving for critically ill patients It will prob ably be shown that symptomatically and with regard to roentgen observations conversion of sputum cavity closure etc improvement in the early months of antimicrobial ther apy with steroids will be slightly better than without But this slight difference would not warrant routine steroid therapy

A few studies on pneumothorax with antimicrobial ther apy suggest that complications are far less frequent and se rious under the *protection of drugs* The *mild renascence in* thoracoplasty is not supported by the author in view of other

currently available methods of treatment In the field of lung resection no satisfactory study as to indications has been carried out The primary indication is a persistent cavity and positive sputum It is seldom necessary to wait longer than 6 months before making the decision concerning resection

The value of rest therapy is small relative to that of drugs and certain surgical procedures Little restriction of physical activity is required though this does not exclude ho pitaliza tion which most patients with active tuberculo is require The corollary to less rest is the lessened need for what has been called rehabilitation

A follow up study of patients treated in 1951 with strepto mycin PAS for an average of 9 12 months revealed that after 1 and 2 years of observation about 20% had died (not all of tuberculous causes) and about 20% of the survivors still had tuberculous disease judged to be active These results were found to relate to the age of the patient and size of the largest cavity at the start of treatment Tuberculous death exceeded expected deaths particularly in the first 3 years after start of treatment This demonstrates the need to con centrate greater therapeutic efforts on the older age groups and patients with larger tuberculous cavities

► [These remarks of Tucker relieve the editor of any necessity to con tribute an editorial note on the present status of tuberculosis therapy The main facts are all clearly stated and conclusions soundly drawn One can do no better than to follow these recommendations —Ed]

Controlled Trial of Chemotherapy in Pulmonary Tuberculosis of Doubtful Activity Report from Research Committee of Tuberculosis Society of Scotland[6] is presented on 189 pa tients with doubtfully active pulmonary tuberculosis who were allocated at random into two groups In 94 treatment was with sodium PAS 5 Gm combined with isoniazid 100 mg twice daily for at least 6 months and 95 were not treated All participated for at least 1 year

Radiographically the estimated cumulative deterioration was 12 6% in the controls compared with 8 1% in the treated group Only 6 of 7 patients who showed deterioration in the treated group had failed to take their drugs as directed To tal deteriorations radiographic and bacteriologic were 17 8% in the controls and 8 5% in the treated group By life table methods x ray improvement at 2 years was estimated

(6) T ber I 39 1 9 137 J 1958

at 31% in the treated group compared with 18% in the controls Most improvement or deterioration occurred in the first 18 months of observation

Chemotherapy is not recommended for all patients with doubtfully active disease because some will fail to take their drugs Over all decrease in the relapse rate may be relatively small nevertheless chemotherapy should be given to certain types of patients at greater risk of relapse

► [Undoubtedly there would be fewer patients failing to take their medication if this consisted of just isoniazid There is little evidence that disease of this extent and character (presumably for the most part noncavitary) is treated more effectively with isoniazid and PAS than with isoniazid alone (see previous paper) Why then add the PAS? There is rarely any difficulty in maintaining patients on a simple regimen of isoniazid but add PAS and there will inevitably be many lapses There can be small doubt that a greater advantage of treatment would have been demonstrated had PAS been left out of the regimen This suggestion is of course still rank heresy to many and it is not to be construed as criticism of the study which was designed along orthodox lines and as such it is admirable and breaks new ground in approaching an important problem of prevention —Ed]

Fate of Patient with Persistent Cavitation and Noninfectious Sputum (Open Negative) after Discharge from Hospital was investigated by R F Corpe and F A Blalock[7] (Battey State Hosp Rome Ga) in 101 men and 58 women who had been on home care for 3-48 months The ratio of Negro to white patients was 95 64 The lesions were all stable on roentgen examination While in hospital all but 7 patients received isoniazid containing regimens for a considerable period Only 3 were advised to take streptomycin PAS as a postsanatorium drug regimen whereas 153 had isoniazid PAS and 3 had isoniazid streptomycin

Mortality rate was 3 8% and reactivation rate 8 8% No additional bouts of suppuration or hemorrhage were reported There was no discernible difference in the incidence of reactivation between the Negro and white patients 13 of 14 reactivations affected men Only 2% of patients were confined to their homes because of physical disability Over 25% were working full time and 45% had unlimited activity

Results show that patients with the open negative syndrome do not create a public health problem in their home environment The authors believe that many of these patients should be continued on drug therapy indefinitely though each case should be judged individually There were

(7) Am R T be 77 764 777 M y 1958

no reactivations among 38 patients whose drug therapy was terminated

Open Healing of Tuberculous Cavities Results in 40 Patients Treated Conservatively are reported by T M Wilson L Doyle and M P Gardiner[8] (Manchester England) The patients were observed for 1½ 5 years A triple drug regimen for at least the 1st year of treatment was used for 32 patients This consisted of a daily intramuscular injection of 1 Gm streptomycin with 10 Gm PAS and oral isoniazid 0 2 Gm daily in 2 divided doses Varying drug combinations were given to 8 patients

In all patients the sputum became negative within 15 months and remained so despite the persistence of cavitation Secondary infection during the 4th year of treatment in a cavitated lobe of 1 patient was the only late complication observed

These results do not support Raleigh s (1957) adverse findings but this is not surprising as his patients received insufficient chemotherapy to validate the observations Extensive disease can be controlled and rendered noninfectious with adequate chemotherapy These findings confirm the claim of Corpe and Stergus (1957) that a regimen of streptomycin PAS and isoniazid is the most effective drug combination in present use Adequate statistical proof of this contention however has yet to be reported It is felt that in certain patients pulmonary cavitation does not necessitate surgical treatment

Influence of Maximum Level of Free Isoniazid in Serum on Structure of Isoniazid Resistant Strains Appearing during Isoniazid Therapy Study of Resected Cases showing a positive culture from one or more tuberculous lesions is reported by G Canetti and J Grosset[9] (Pasteur Inst Paris) There was a significant correlation between the maximum level of free isoniazid of the serum and base resistance (i e maximal concentration of isoniazid to which 100% of bacilli of the strain are resistant) in the 94 cases studied When the concentration of isoniazid was weak base resistance of strains was sometimes low sometimes increased When isoniazid level was high base resistance of strains was almost always increased

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(8) Brit M J 1 47 90 J 1 1 1958
(9) P t ber 1 s 2 778 806 A g Sept 1958

Except in rare and doubtful instances when the number of bacilli present in the lesion is high only mutants having a superior resistance to the maximum content of free isoniazid in serum can multiply during isoniazid therapy The rule is less certain when the number of bacilli in the lesion is small i e when multiplication of bacilli has apparently been arrested for a long time In such instances exceptions become more frequent showing that isoniazid sensitive bacilli with inferior resistance to the maximal concentration of free isoniazid may well survive in tuberculous lesions during isoniazid therapy Even in these cases the bacilli encountered have most often a base resistance superior to the free isoniazid content of the serum

Most isoniazid resistant strains contain in variable proportions mutants with resistance higher than the base resistance of the strain There is no significant correlation between these mutants and the maximal level of free isoniazid

Influence of duration of isoniazid therapy on base resistance of resistant strains is relatively less significant When maximal content of free isoniazid is low strains of the same base resistance are found with treatment periods exceeding 2 years When isoniazid content is high strains of the same high resistance may be found with treatment periods of less than 6 months When isoniazid level is medium or average there is a slow increase of base resistance of bacterial strains with prolongation of treatment After the first 6 months of treatment effect of maximal level of serum isoniazid on base resistance of organisms appears more potent than that of treatment duration

In 178 resected cases (84 with negative and 94 with positive cultures from the lesions) there was no correlation between maximal level of free isoniazid in serum and incidence of sterile cases

Corticotropin and Corticosteroid Therapy in Tuberculosis is evaluated by Roger M Des Prez and Avrum Orcanick[1] (Cornell Univ) The dramatic symptomatic improvement effected by corticotropin in other infectious diseases has led to its early trial in human tuberculosis Abrupt decrease in fever and toxicity increase in appetite and sense of well being and in some patients improvement in x ray findings and in the extent of laryngeal involvement have been noted

(1) A M A Arch Int Med 101 11 9 114 J 1958

no reactivations among 36 patients whose drug therapy was terminated

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(8) Brit M J 87 90 Jul 12 1958
(9) R ubec Fa s 778 806 Aug 5 pt 1958

On withdrawal of the hormone the clinical state has re turned to pretreatment levels after a sometimes marked re bound elevation of temperature Treatment periods had been brief and it was not clear whether or not the hormone had an untoward effect on clinical courses as a whole However there soon began to appear case reports of rapid exacer bation of latent tuberculosis during hormone treatment for other disorders

The authors studied 3 females aged 13 44 and 1 man 45 who had widespread pulmonary tuberculosis with severe toxicity Marked respiratory insufficiency was present in 2 Steroid therapy was successful in all from the beginning Of the 4 patients 1 received ACTH gel 40 units twice daily which gradually was tapered until discontinued after about 6 weeks 1 received cortisone 300 mg on the 1st day and 100 mg daily for 26 more days 1 was started on hydrocorti sone 80 mg/day which dose was gradually reduced to 5 mg/day and discontinued after 7 weeks and 1 received cor ticotropin All also were given antituberculous drugs

When combined with effective antimicrobial therapy use of corticotropin and cortisone in tuberculosis is safe In pa tients with marked toxicity in complicated tuberculous men ingitis and in severe reactions to antituberculous chemo therapeutic agents there are definite and sometimes urgent indications for administration of corticotropin and cortisone Their use in serous membrane tuberculosis endobronchial tuberculosis and uncomplicated pulmonary tuberculosis seems promising

Treatment of Tuberculous Pleural Effusions with Partic ular Reference to Adrenal Corticosteroids Margaret H D Smith and Nicholas Matsaniotis[2] report the results of treat ment in the Chest Clinic of the Children s Medical Service o Bellevue Hospital during the past 25 years Of 176 patients with primary tuberculous pleural effusion 5 1% died of tu berculosis In 5 7% chronic pulmonary tuberculosis devel oped later and in 3-4% extrapulmonary tuberculous compli cations developed In 66 of the patients pleural thickening remained visible in x rays for up to 22 years and in 4 5% the effusion was considered a factor in the later development of mild or moderate scoliosis

Two considerations in the management of tuberculous

(2) Pediatrics 22 1074 1087 December 1958

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Two considerations in the management of tuberculous

(2) Ped t ics 22 1074 1087 Decembe 1958

vestibular apparatus or hemopoietic system Other than eosinophilia which was common no sensitivity phenomena of significance were observed Bacterial resistance was present at 60 days in half the patients and at 120 days in all Clinical and roentgenographic evaluation indicated that kanamycin had some antituberculous activity and that in combination with another antituberculous agent it should be given a trial in a larger series of patients

Kanamycin inhibited the growth of a strain of photochromogenic acid fast bacilli This finding suggests that the drug also be given further trial in the treatment of diseases associated with atypical acid fast bacilli

The mechanism of the hearing loss in 2 patients is not apparent Neither age nor total dosage of drug administered is likely to be the sole factor involved in this form of drug toxicity since other patients in the same general age group received larger doses of the drug The finding of granular casts in the urine of all patients is probably not on the basis of impurities since kanamycin is said to be a crystalline material of a high degree of purity The frequent occurrence of eosinophilia suggests that hypersensitivity reactions may be anticipated with kanamycin

The rapid appearance of strains of tubercle bacilli highly resistant to kanamycin makes it obvious that if prolonged usage is contemplated attempts will have to be made to delay this resistance by the concomitant use of another antituberculous agent

► [Other trials indicate that the toxicity of kanamycin is considerable It seems unlikely that this will prove to be a drug of great usefulness in tuberculosis —Ed.]

Observations on Antituberculous Effectiveness of Alpha Ethyl Thioisonicotinamide in Tuberculosis in Humans G Brouet J Marche N Rist J Chevallier and G LeMeur[4] (Paris) investigated the use of alpha ethyl thioisonicotinamide in 102 patients with pulmonary tuberculosis In 78 the drug was administered either alone or with another antimicrobial drug for 3 months or more The tuberculosis was relatively recent in 43 of these and chronic in 35

The drug was often badly tolerated and caused anorexia nausea or gastric irritation accompanied by a cessation of weight gain or an actual loss of weight There was no evidence that the drug was toxic for the liver kidneys or hemo

(4) Am Rev Tuberc 79 6-18 Jan y 1959

poietic system Its neurotoxicity appears to be minimal and requires special attention only in patients treated simultaneously with isoniazid or cycloserine The drug improved the clinical roentgenographic and bacteriologic findings In many patients with recent disease infectiousness was reversed within 2 3 months

Within the period of observation the drug s action was not constant A lack of improvement and the appearance of resistant strains were observed in several patients In these the tubercle bacilli had maintained susceptibility to other antimicrobials and a change of treatment brought favorable therapeutic results It is believed however that the drug should not be used alone in the initial treatment of recently developed pulmonary tuberculosis but should be administered along with isoniazid The results obtained when alpha ethyl thioisonicotinamide was used in multiple drug regimens including isoniazid or isoniazid and streptomycin were most satisfactory

One of the most difficult therapeutic problems today concerns patients with chronic pulmonary tuberculosis who have not responded satisfactorily to treatment In most of these patients the lesions existed before the days of antimicrobial therapy or are in relapse Such lesions are extensive generally bilateral and with large cavities consistently discharging tubercle bacilli resistant to streptomycin and isoniazid Some of the patients may be satisfactorily managed by a combination of medical re treatment along with judiciously timed surgery Cycloserine viomycin and alpha ethyl thioisonicotinamide in different regimens according to previous treatment received and to the bacteriologic data may produce reversal of infectiousness

► [The problem with this drug appears to be primarily one of gastrointestinal intolerance If means can be found to overcome this difficulty it may yet be a valuable addit on —Ed]

Pulmonary Tuberculosis and Partial Gastrectomy J A Balint (London) studied the mortality due to pulmonary tuberculosis in 2 413 patients (2 065 men 348 women) followed for 4 15 years after partial gastrectomy for peptic ulcer The conclusion of previous authors that pulmonary tuberculosis constitutes a risk of partial gastrectomy was confirmed Postgastrectomy pulmonary tuberculosis represents about 5% of new notifications in adult men in England

(5) G t oe t l g 90 65 84 1958

and Wales Explanation for the increased incidence of pulmonary tuberculosis after partial gastrectomy for peptic ulcer may be found in the interaction of several factors such as presence of an unduly large reservoir of quiescent pulmonary tuberculosis in men with chronic peptic ulcer mild malnutrition due to the ulcer itself and to subsequent partial gastrectomy the concentration of men with gastric ulcers in the lower social classes heavy tobacco consumption and the age at which partial gastrectomy is commonly carried out in men with peptic ulcer

Pulmonary tuberculosis after partial gastrectomy may be prevented by preoperative x ray of the chest to insure diagnosis and treatment of any active tuberculosis present by proper nutrition pre and postoperatively and by discouraging cigarette smoking Malaise tiredness and weight loss after gastrectomy should not be attributed to postgastrectomy syndromes until tuberculosis has been excluded by adequate diagnostic studies

Chronic Pulmonary Disease Due to Atypical Acid Fast Bacilli In the laboratory at the Southwest Florida Tuberculosis Hospital which is the central laboratory for all 4 Florida state tuberculosis hospitals Albert G Lewis Jr Frank P Dunbar Elizabeth McAlister and Robert Cacciatore[6] (Tampa) isolated the following groups of acid fast organisms (1) photochromogens which are pathogenic (2) nonphotochromogens which as a group are still under study as to pathogenicity and (3) scotochromogens which are considered saprophytes except under certain conditions when they may be pathogenic the consensus being that they are invaders to tuberculosis silicosis and other chronic lung conditions

The authors isolated 80 strains of atypical acid fast organisms avirulent for guinea pigs and of varying pathogenicity for mice When a culture is thought to be atypical instead of Myobacterium tuberculosis a smear is made from the suspected colonies which appear on primary isolation on Lowenstein Jensen s medium Although atypical organisms have certain characteristic features on smear this is not dependable and subculture is necessary Atypical organisms are then subjected to a number of in vitro and in vivo tests The most important is the test for the type of pigment pro

(6) South M J 51 1241 1250 Oct be 1958

CHARACTERISTICS OF ATYPICAL MYCOBACTERIA COMPARED WITH THO E OF MYCCBACTERIUM TUBERCULOSIS VAR HOMINIS

	M T	T e Aty ic l Acid-Fast O g t					
		Pl t l m g		N ph t ch m g		Sc t h m g	
C l y sm th	R gh	U lly ooth		S th		S ooth	
G wt							
20 C	N		Sl w		Sl w		Sl w
37 C	Sl		Sl w		Sl w		Sl w
I gm t t							
(w l ght	B ff		Y ll w		B ff		O g
C d k	B ff		B ff		B ff		Y ll w-c g
C t l t ty	3+		4+		4+		4+
C d f m t	4+	— t	+		—		—
A m l l							
(r g	4+		—		—		—
Ho e	4+		3+	3+ t	—		—
D s t e							
l t th py							
SM	—	+	—	+	—	+	—
PAS	—		+		+	+	—
INAH	—	+	—		+	+ o	—

duction when grown in the light and in the dark and the abil ity of the organism to grow at room temperature The cata lase test test for serpentine cord formation and neutral red test have also been used Drug susceptibility tests have been done routinely with isoniazid PAS and streptomycin two concentrations each (table) For 20 of the strains drug sus ceptibility tests were done using various other antibiotics

The table shows in graphic form the difference in multiple characteristics between tubercle bacilli and atypical acid fast bacilli when subjected to these tests Increased catalase ac tivity in the case of atypical organisms would serve to dif

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(6) South M J 51 1241 1250 Oct ber 1958

daily There was a dramatic reduction in dyspnea in 24 hours after therapy was begun Within a few days the patient began to eat and was removed from the oxygen tent Chest x rays taken 5 months later showed complete disappearance of the original shadows The patient returned to work and has remained well for the past 18 months

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SARCOIDOSIS

Further Study of Kveim Reaction in Sarcoidosis and Tuberculosis Conflicting reports on the specificity and reliability of the Kveim reaction induced Harold L Israel Maurice Sones Herman Beerman and Thomas Pastras[8] (Univ of Pennsylvania) to test 60 patients with sarcoidosis and 40 with pulmonary tuberculosis The test material was injected

RESULTS OF KVEIM TESTS 1954-57

Year	Test Material	Patients with Sarcoidosis		Patients with Tuberculosis	
		No. Completing Test	No. Positive	No. Completing Test	No. Positive
1954-55	A	57	12 (26 1%)	33	14 (42 4%)
1956-57	D	46	13 (28 3%)	29	0
1956 57	Other investigators	19	5 (26 3%)	6	0

intracutaneously as superficially as possible Biopsy specimens were obtained 8 weeks after injection by the punch technic

Results with current test material (D) differed notably from those obtained with the test material (A) prepared 2 years earlier from lymph nodes excised from the same patient (table) In both studies about 25% of patients with sarcoidosis had positive reactions None of the tuberculous patients in the current series had positive reactions in contrast to 42 4% of the group tested with the initial material

Variability of the test material appears to be the principal cause of these inconsistent results Differences in histologic interpretation also contribute to the difficulties encountered with this test whereas the type of clinical material studied appears to be a minor factor

The Kveim reaction is an immunologic phenomenon In

(8) New England J Med 259 365 369 Aug 21 1958

ferentiate them from isoniazid resistant mutants and cultural characteristics and other laboratory procedures will differentiate them from other pathogenic and frankly saprophytic mycobacteria Susceptibility studies revealed resistance to partial resistance of the nonphotochromogens in isoniazid PAS and streptomycin Drug susceptibility is variable in cases of photochromogens and scotochromogens Susceptibility studies indicate that some of the short term adjuvant drugs may be of more value than the major drugs

All 37 patients from whom atypical organisms were isolated had abnormal chest x ray findings In view of the isolation of these three types of atypical organisms from sputum repeatedly from multiple areas of resected lung including both cavitary and nodular lesions and at autopsy from multiple areas and in the absence of other demonstrable causative agents it may be concluded that under certain circumstances photochromogens nonphotochromogens and scotochromogens may cause chronic pulmonary disease which is pathologically radiologically and symptomatically similar to pulmonary tuberculosis

► [*The growing importance of the recognition of these atypical mycobacteria is here further documented Similar findings are being reported from many different parts of the country* —Ed]

HISTOPLASMOSIS

Acute Disseminated Pulmonary Histoplasmosis Treated with Cortisone and MRD 112 (beta diethylaminoethylfencholate) is reported by Andrew S Tegeris and David T Smith[7] (Duke Univ) Most patients with the epidemic type of pulmonary histoplasmosis recover without specific treatment

Man 32 had almost complete consolidation of the lung which threatened his life Because of a strongly positive skin test to histoplasmin it was assumed that a considerable part of the pulmonary infiltration was due to an allergic reaction to histoplasmin in the lungs Cortisone was given to suppress the allergic reaction In an effort to prevent dissemination of the fungus that sometimes occurs after cortisone therapy MRD 112 was given The dose was 300 mg dissolved in 300 ml of 5% dextrose in saline or 5% dextrose in distilled water and it was given by slow intravenous drip over 3 5 hours

(7) Ann Int Med 48 1414 14 0 J ne 1958

mild renal insufficiency in 3 of them (see table) The increase in blood urea during the early phase of treatment was alarm ing Possibly it represents an increased renal load associ ated with the protein catabolic effects of the steroids In view of the calcium deposits found in the renal biopsy tis sue from the first patient perhaps the persistence of renal insufficiency in 3 patients can be attributed to microscopic nephrocalcinosis

The incidence of hypercalcemia in sarcoidosis has been estimated as 20 30% The cause of the hypercalcemia has re mained obscure There is lack of correlation between serum protein and serum calcium values Originally it was thought that hypercalcemia was found only when hyperproteinemia was present Subsequent observations have failed to verify this association The values of serum proteins were normal in 3 of the study patients Again hypercalcemia has been an inconsistent finding when roentgenographic evidence of bone lesions has been seen in patients with sarcoidosis Hy peractivity of the parathyroid glands has been postulated as a possible cause but most observers have reported that the parathyroid glands were normal on exploration of the neck or at autopsy

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WEGENER S GRANULOMATOSIS

Wegener s Granulomatosis is characterized by a necro tizing granulomatous lesion in the upper airways or lower respiratory tract or both generalized focal vasculitis and necrotizing glomerulitis Bernhard Chomet Clifford G Pilz Kenneth Vosti and Victor Levine[1] (VA Westside Hosp Chicago) observed this syndrome in a man 26 with an al most continuous fever which was unaffected by various anti biotics Tongue ulcers developed and were characterized by extreme pain The pulmonary lesion expanded rapidly and was accompanied by chest pain and hemoptysis The patient died 5½ weeks after admission Only in the latter part of the hospital stay was the general systemic nature of the dis ease apparent Although the kidneys were directly respon sible for death in 86% of reported cases such did not seem to

(1) A M A A h P th 66 300 307 J ly 1958

its present form however the test is not sufficiently reli able to justify its use as a substitute for clinical and biopsy methods of diagnosis

Effect of Steroid Therapy on Hypercalcemia and Renal Insufficiency in Sarcoidosis was studied by Donald A Scholz[9] (Mayo Clinic) in 4 men aged 25 68 The predominant com plaints were anorexia nausea vomiting and abdominal pains simulating ulcer distress The diagnosis of sarcoidosis was confirmed in each patient by lymph node biopsy Steroid

SIGNIFICANT BIOCHEMICAL ALTERATIONS IN FOUR CASES OF SARCOIDOSIS WITH HYPERCALCEMIA AND RENAL INSUFFICIENCY BEFORE AND AFTER STEROID THERAPY*

Patient		Calcium Level Mg per 100 Ml of Serum		Phosphorus Level Mg per 100 Ml of Serum		Urea Level Mg per 100 Ml of Blood	
Case	Age	Before	After	Before	After	Before	After
1	48	12 5	10	4 2	2 9	1 8	68
		12 4	10 1	4			
2	59	14 4	10 6	4 2	3 1	4	84
		13 8		4 9		9	
3	68	11 1	9 4	4 6	3 0	8	118
		11 9		3			96
		1 6					
4	2	13 1	10 4	3 8	2 3	8	31
		12	10		2.5		

*All p t t w r men

therapy was started in 2 patients with 200 mg cortisone in 1 patient with 30 mg prednisone and in 1 with 20 mg pred nisone daily The steroids produced a prompt fall in the level of serum calcium with complete relief of symptoms despite evidence of persistent mild renal insufficiency in 3 cases Long term steroid therapy with 2 5 7 5 mg prednisone daily was necessary to maintain an asymptomatic and nor mocalcemic state The significant biochemical alterations before and after steroid therapy are listed in the table

Balance studies carried out in 2 patients revealed hyper calcemia hypercalciuria and low fecal calcium content In both cortisone produced a prompt fall in the level of serum calcium a decrease in urinary excretion of calcium and a sub sequent increase in fecal calcium There was an accompany ing fall in the level of serum phosphorus with increase in urinary and fecal excretion of phosphorus

Steroids produced marked decrease in the serum phos phorus in every patient despite the persistent evidence of

(9) J A M A 169 68 657 Feb 14 1959

mild renal insufficiency in 3 of them (see table) The increase in blood urea during the early phase of treatment was alarming Possibly it represents an increased renal load associated with the protein catabolic effects of the steroids In view of the calcium deposits found in the renal biopsy tissue from the first patient perhaps the persistence of renal insufficiency in 3 patients can be attributed to microscopic nephrocalcinosis

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(1) A.M.A. Arch. Path. 66:100-107, July 1958

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1	48	12.[illegible]	10	4	2 9	1.8	68
		12 4	10 1	4			
2	9	14 4	10 8	4 2	3 1	4	84
		13.8		4 9		9?	
3	68	11 1	9 4	4 6	3 0	8	118
		11 9		3			96
		1 6					
4	–	13 1	10 4	3.8	2 3	8	84
		1	10				

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(9) J A M A 169 #3 647 Feb 14 1959

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(1) A M A A h P th 66 100 107 J ly 1958

hold true in this patient whose preterminal nonprotein nitrogen was not markedly elevated

Notable findings at autopsy were necrotizing granulomatous process in lung and spleen diffuse ulcerative and necrotizing bronchitis small granulomatous lesions diffusely infiltrating the liver focal necrotizing glomerulonephritis and focal vasculitis

Pathergic Granulomatosis (Wegener s Granuloma) of Lung Five Cases of Similar Clinical Courses and Pathologic Findings R Maurice Hood Hugh V O Connell and Don L McCord (US Naval Hosp Oakland Calif) studied 3 men and 2 women under age 35 with pathergic granulomatosis X rays revealed diffuse fine nodular pulmonary infiltrations in all Three patients were asymptomatic during the entire period of observation One patient had malaise fever and weight loss for 4 months before hospitalization but became asymptomatic without any specific therapy and 1 was hospitalized with severe pain in the right scapular region

Four patients presented no evidence of involvement by a granulomatous process of the upper respiratory passages kidneys the vascular system outside the lung or of any other organ system The other patient had a solitary rib lesion histologically typical of eosinophilic granuloma Respiratory ventilation studies in 3 patients showed no marked ventilatory defect

Each patient had a lung biopsy All specimens showed granulomatous foci the striking features being eosinophilia and angiitis The rib lesion found in 1 patient was identical histologically with the pulmonary lesion Despite the angiitis present in all patient necrosis was not a prominent feature The inflammatory reaction in the vessel walls was characterized by polymorphonuclear and round cell infiltration in all layers Endothelial proliferation was present in some The bulk of the granulomatous masses was composed of aggregates of epithelioid cells macrophages lymphocytes plasma cells and myriads of eosinophils The surrounding lung parenchyma not involved in the granulomatous process showed some alveolar distortion and compensatory emphysema

Most of the reported cases of Wegener s granuloma have ended fatally and been diagnosed on autopsy Histologically

(2) A R Tube c 78 21 37 July 1958

the authors cases were strikingly similar to those reported as Wegener s granuloma but clinically the course was be nign

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INFLUENZA AND ITS COMPLICATIONS

Studies on Influenza in Pandemic of 1957 58 II Pulmonary Complications of Influenza Donald B Louria Herbert L Blumenfeld John T Ellis Edwin D Kilbourne and David F Rogers[3] (New York Univ Bellevue Med Center) report results of a study in 33 patients

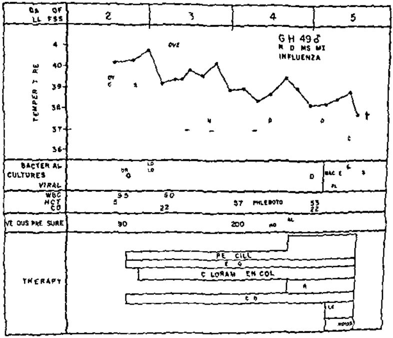
Man 49 was hospitalized because of fever and progressive respiratory difficulty of 20 hours duration He appeared cyanotic extremely dyspneic and critically ill Chest x rays (Fig 31) revealed an exten



Fig 31 – Adm h t x y n m w h p ma y fl zal pneumonia pe imposed h m h t d w th m t l tenos an l ff y Den ty in right m dl g fi ld ep ts loculated i t l b ff on th t w s p t bef e t l ((C rt y f Lo n D B t / J Cl n I t 38 (p 2) 213 65 Ja ry 19 9)

(3) J Cl I t 38 (pt 2) 213 265 J ry 1959

sive bilateral diffusely nodular infiltrate fanning peripherally from the hilar regions The patient s course is depicted in Figure 32 He was placed in an oxygen tent and treated with penicillin streptomycin and chloramphenicol Administration of morphine sulfate digitoxin diuretics aminophylline and Vaponephrin* by nebulizer did not notably improve the respiratory distress His blood pressure became unobtainable 72 hours after hospitalization Despite intensive



F g 32—Cou s f illn (Cou te y f Lou D R t al J Cl n I vest 38 (pt 2) 213 265 J nuary 1959)

therapy which included hydrocortisone and levarterenol the patient died on the 4th hospital day

At autopsy the significant findings were confined to the lungs and heart The heart showed changes characteristic of rheumatic heart disease with severe mitral stenosis The lungs were intensely engorged and weighed 4 000 Gm Th parenchyma throughout all lobes was dark red and subcrepitant and large amounts of thin blood tinged fluid flowed from the cut surface Influenza A virus Asian type vas recovered from lung tissue

The disease in the 33 patients could be categorized into several syndromes (Fig 33) (1) In 3 patients transient pulmonary signs vere detected in the absence of x ray signs they recovered on symptomatic treatment alone (2) In 15

patients secondary bacterial pneumonia arose relatively late in the course of influenza The course of infection and response to therapy in these patients did not differ materially from that of uncomplicated bacterial pneumonia (3) In 9 patients laboratory and clinical study indicated that concomitant infection with influenza virus and bacteria was responsible for the pneumonia observed (4) In 6 patients fulminating diffu e hemorrhagic pneumonia was noted all

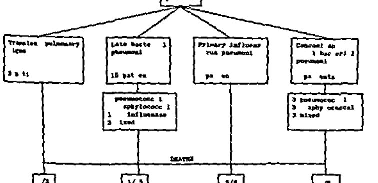


Fig 33 —P lm y omplc t of fl en ~ w Y k Hosp t l, (2 1 t d ths a soc t d w th i ll) (Co rte y of Lo D B t l J Cl n I t 38 (pt 2) 213 6 J u ry 19 9)

but 1 died No pathogen other than influenza virus could be related to this abacterial syndrome

Of the 35 patients 24 had chronic underlying disease or were pregnant Of the 30 with roentgenographically confirmed pneumonia 21 had pre existing illness or were pregnant Of these 21 14 had underlying cardiac disease that was of rheumatic origin in 10 Eleven patients died 9 of whom had underlying disease 5 of the 9 had rheumatic heart disease

► [This experience differs with most other reported studies of the recent pandemic in regard to the appreciable number of patients who had a fulminating usually fatal pneumonia from which no pathogen other than influenza virus could be recovered The experience however is not unique (see *next paper*) The occurrence of such pneumonias unassociated with secondary bacterial *infection has been almost exclusively in patients with* mitral heart disease Louria and his associates feel that despite this association and the common resemblance of the roentgenographic picture to

pulmonary edema these cases are instances of a true influenzal virus pneumonia Newcombe and his group (next paper) regard the association as unexplained but also consider that a direct attack of the virus on the alveolar and capillary walls may be responsible for the pulmonary edema. The syndrome has also been reported from The Netherlands (Hers Gosling Masurel and Mulder Lancet 2 1164 1957) —Ed]

Influenzal Pneumonia in Mitral Stenosis was observed by C P Newcombe P G F Nixon and H Thompson[4] in 9 patients (table) The illness was characterized by rapid development of pulmonary symptoms 5 patients became critically ill within 24 hours of onset This rapid course did not suggest primary virus infection followed by pneumonia

CHIEF CLINICAL FEATURES

Case no.	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Sex	F	M	M			M		F	
Age	39	30		30	5[illegible]	49	50	[illegible]	[illegible]
Haemoptysis	Fluid	Froth		Blood	F[illegible]	Blood	Frothy	Streaks	— Froth
Heart lesion	M.	M.	M.R.		M.		M.		M.
R.V. Hypertrophy									
Previous dyspnea grade	1					4		1	
Maximum temperature / W.B.C.	103	102	104 / 3,[illegible]		10,[illegible]	9,500	103 / 8,[illegible]	104	101 / 6,[illegible]
Complications		—			[illegible]		[illegible]	—	—
Outcome	D	S			D				

A = alive A I = aortic incompetence A F = auricular fibrillation A S = aortic stenosis D = dead M I = mitral incompetence M S = mitral stenosis Numerical grading after Wood (1956)

Hemoptysis which persisted from 3 7 days occurred in two forms as fluid blood of over 2 oz a day or as frothy blood filling several 5 oz cartons daily Physical examination showed the patients were severely ill with dyspnea cyanosis and high fever Signs of consolidation did not develop

Radiologically the lung fields appeared as multiple large ill defined opacities usually asymmetrically distributed and associated with clouding of the intervening lung In some patients the appearance resembled acute pulmonary edema and in others it was difficult to distinguish from pulmonary infarction In patients who recovered the x ray appearance of the lungs became normal in 2 3 weeks

Little assistance was obtained from other routine investigations Antibiotics were helpful in only 2 patients The association between mitral stenosis and influenzal infection remains unexplained

(4) Act med [illegible] 162 441 447 1958

Lung Abscess and Pneumonia Complicating Influenza J M Angeloni and G W Scott[5] studied 41 patients hospitalized with pneumonic complications of influenza Thirteen aged 47 83 had pre existing chronic chest disease They presented clinical and radiographic pictures of bronchopneumonia which developed 1 4 days after onset of influenza Staphylococcus aureus was cultured from the sputum in only 1 Of these patients 6 died and 7 made good recovery

In 28 patients aged 13 68 who were previously fit symptoms of pneumonia developed 1 14 days after onset of influenza In 14 Staph aureus was cultured from the sputum and in 6 instances it was insensitive to penicillin In 15 recovery was uneventful in 2 there was slow resolution associated with pleural effusion 3 died of fulminating influenzal pneumonia and in 8 lung abscesses developed The abscesses varied from a single lesion to multiple cavities throughout both lungs In 1 patient there was an associated empyema Physical chest signs were often inconspicuous Six patients were extremely ill on hospitalization with high fever tachycardia dyspnea cyanosis and often delirium Leukocytosis was present in 3 and arose later in 3 more with the development of lung abscess The highest total leukocyte count was 21 000

Coagulase positive Staph aureus was cultured from the sputum in 6 patients and was resistant to penicillin in 3 In 1 patient beta hemolytic streptococcus was repeatedly found in sputum cultures and in another no pathogens were isolated

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PARASITIC DISEASES OF THE LUNG

Chronic Pulmonary Schistosomiasis is discussed by Z Farid J W Greer K G Ishak A M El Nagah P C LeGolvan and A H Mousa[6] The schistosoma ova but rarely the adult worms reach the pulmonary circulation from the veins of the bladder and intestine via the internal iliac veins and the portacaval anastomosis respectively There the ova as emboli obstruct the pulmonary arterioles and initiate a tissue reaction outside the arteriolar wall

(5) La et 1 1254 1 56 J 14 1958
(6) Am R T be 79 119 133 F b ry 1959

which results in formation of a granuloma The vascular lesions result from passage of ova through the arteriolar walls with resultant inflammation and necrosis Resolution and healing of this inflammatory process lead to narrowing thickening, and partial or complete occlusion of the pulmonary arteriole Later angiomatoids may develop from canalization of the fibrous tissue obstructing the vessel When such vascular lesions become widespread a diffuse endarteritis obliterans results A definite restriction in the capacity of the pulmonary vascular bed occurs and consequently the pulmonary pressure rises The pulmonary artery dilates and may reach aneurysmal size The right ventricle of the heart may fail after dilatation and hypertrophy Secondary superimposed arteriosclerotic changes in the wall of the pulmonary artery may ensue The parenchymatous lesions are the extravascular granulomas

Pulmonary function tests on 15 patients demonstrated three main clinical types of ventilatory insufficiency In 3 patients obstructive ventilatory insufficiency was seen They had a decreased maximal breathing capacity a normal total vital capacity but a retarded timed vital capacity The residual volume was increased and the ratio of residual volume to total lung capacity × 100 varied between 35 and 38% In 3 other patients pulmonary function tests demonstrated a restrictive type of ventilatory insufficiency characterized by a reduction in the total lung capacity with a decreased total vital capacity and a normal timed vital capacity The maximal breathing capacity was normal or only slightly decreased The residual volume was normal and the ratio of residual volume to total lung capacity × 100 was below 25%

In 4 patients combined obstructive and restrictive ventilatory insufficiency was demonstrated the pulmonary function tests being characterized by a decreased maximal breathing capacity and a reduction of the total vital capacity and timed vital capacity Residual volume was slightly increased and the ratio of residual volume to total lung capacity × 100 varied between 26 and 58% In 2 patients the only pulmonary function defects were a delayed timed vital capacity In 1 patient the pulmonary function tests were normal

Treatment of Eosinophilic Lung (Tropical Eosinophilia) with Diethylcarbamazine was studied by T J Danaraj[7] (Univ of Malaya) in 110 patients Initially dosage of di ethylcarbamazine was 4 mg /kg body weight given 3 times daily for 4 days to 46 patients Later two large doses were tried 6 mg and 10 mg /kg body weight given 3 times daily for 5 days to 57 and 7 patients respectively Average total adult dose for each of the three dosage schedules was 3 200 6 000 and 10 000 mg respectively The drug was given after meals in 50-mg tablets the syrup was used for children Except for 11 patients who showed severe bronchial spasm and were treated with antispasmodics as well the patients were given only diethylcarbamazine Follow up varied up to 14 months

The criteria of cure were amelioration of symptoms dis appearance of physical signs in the chest decrease in the number of circulating eosinophils to below 3 000/cu mm clearing of the x ray picture of the lung and return of the erythrocyte sedimentation to normal

Clinical improvement was noted by 107 patients on the 2d to 4th day after start of treatment while the drug was still being taken and progressed steadily until by the end of the 1st week 59 patients had complete relief and 48 had residual cough only Of the latter group 33 experienced further im provement during the 2d week In most patients the lungs were clear by the 7th day after start of treatment

When the leukocyte count was done on the 3d day of treat ment a marked decrease in eosinophils was found in 98 pa tients in the other 12 an increase was noted on the 3d day followed by a similar rapid decrease on the 5th day Chest x rays taken 1 week after cessation of treatment showed dis tinct improvement in all 109 patients with x ray abnormal ity the striations becoming less prominent with clearing of the pulmonary mottling The eosinophils dropped below 3 000/cu mm

Mild toxic effects were noted in 12 patients and 6 said that they felt a little giddy and had vomited once With the third and largest dosage toxic symptoms were more common (6 of 7 patients) and relatively more severe

Though all three dosages of the drug were effective symp tomatic response was better with the two larger dosages

(7) Q n J M d 27 43 63 April 1958

than with 4 mg /kg body weight given 3 times daily for 4 days The dosage recommended is 6 mg /kg body weight 3 times a day for 5 days

Serologic Diagnosis of Eosinophilic Lung (Tropical Eosinophilia) and Its Etiologic Implications were investigated by T J Danaraj L S Da Silva and John F Schacher[8] (Univ of Malaya) Since recognition of a syndrome charac-

INITIAL FILARIAL COMPLEMENT FIXATION TEST RESULT FOR DIFFERENT STUDY GROUPS

FCFT titers	Study groups						
	1 Hypereosinophilia		2 Mild eosinophilia	3 Human filariasis	4 Dog filariasis	5 Ascariasis	6 Normal
	EL	non EL					
Negative	10	12	79	95	26	28	151
1 5	8	1	2	10	4	1	4
1 10	23	2	2	7	—	1	4
1 20	44	—	2	7	3	—	1
1 40	51	—	—	—	—	—	—
1 80	43	—	—	—	—	—	—
1 160	20	—	—	—	—	—	—
1 320	14	—	—	—	—	—	—
Totals	213	15	8[illegible]	119	33	30	160
% positive	95 3	20 0	[illegible] 1	20 2	21 [illegible]	6 7	5 6

terized by paroxysms of cough with hypereosinophilia that responds favorably to treatment with organic arsenicals many reports have appeared from tropical regions confirming the existence of this clinical entity The syndrome has been variously designated as eosinophilic lung tropical eosinophilia or pulmonary eosinophilosis The clinical picture is distinct in most of these patients but similar symptoms with hypereosinophilia may sometimes be produced in the course of known parasitic infections such as strongyloidiasis schistosomiasis ascariasis visceral larva migrans and pulmonary gnathostomiasis and in allergic conditions such as Löffler s syndrome and in some cases of bronchial asthma Th[illegible] has made diagnosis of eosinophilic lung diffi-

(8) Am [illegible] Trop Med 8 1 1 159 M[illegible] h 1959

cult except on the basis of relief from symptoms and hematologic response after arsenotherapy or treatment with diethylcarbamazine

Reports to date on eosinophilic lung have emphasized the lack of a demonstrable etiologic agent Recently therapeutic results with diethylcarbamazine suggested that the causative agent may be some form of filarial worm Clinically there was no evidence to support this in 110 patients cured with this drug there was neither history of filariasis nor signs of infection and no microfilariae were found in blood samples taken at night using Knott s concentration technic It was therefore decided to examine the serums of subsequent patients for filarial complement fixing antibodies using as antigen 1% alcoholic extract of dried powder of Dirofilaria immitis This complement fixation test was applied to the serums of 228 persons with hypereosinophilia 213 of whom had diagnosis of eosinophilic lung and to various control groups The test was positive (table) mostly with high titer in 95 3% of those with eosinophilic lung whereas in the controls positive reactions in relatively low titers were obtained in only 5 6 21 2%

NEOPLASMS

Behavior of Pulmonary Vessels in Bronchial Carcinoma **Electrokymographic Studies** demonstrate pulsatile density changes in the central and peripheral pulmonary vessels more conveniently than pulmonary angiography since no internal instrumentation is needed J Lissner[9] (Univ Clinic Frankfurt) studied electrokymographically 200 patients with normal chest x rays and 80 with various pulmonary or mediastinal tumors Electrokymograms were taken bilaterally from symmetrical lung fields and the tracings were related to ECG (lead II) and carotid pulse tracings (Fig 34) The normal tracings were similar to those obtained from the pulmonary artery except for the timing and a small or absent deflection Even in normal tracings there were some slight differences between the curves taken from corresponding areas due to oscillatory interference from slight

(9) F rtsch C b R tg t ahlen 89 534 544 N mbe 1958

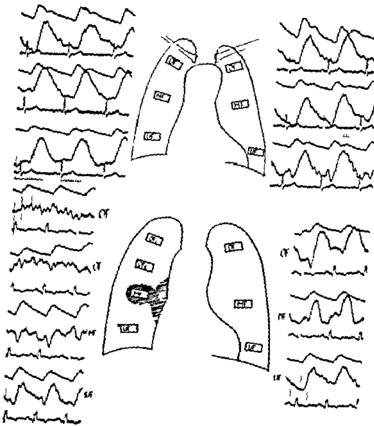


Fig 34 (top) —El t kym graph finding due to s lar de ty ch g periph r l l g fi ld f n rm l p on (l w r t c ng ECG l d II m ddl t a ng l ct okym g am upp t ng c t d pul)

Fig 35 (b tt m) —El t kym g m f p t t w th b h ge c n ight upp l be In ght pp fi ld (OF nd OF) n hythm c curv at MF t nsm tt d aur l m m t In th l ng a th e w e n v scul den ty b ng d monstr ble by l t kym g aphy

(Court sy f L n J k ts h G b R tgen trabl n 89 534 544 No emb r 1958)

movements of the patient and from transmitted movements of the heart and large vessels However changes from inter ference can be easily differentiated from pathologic changes In all 200 patients with normal chest x rays the same tracing characteristics were found in the peripheral lung fields

Figure 35 shows the findings in a patient with broncho genic cancer in the right upper lobe The electrokymogram revealed normal vascular pulsations in the left upper lung field but only atypical curves of minimal amplitude in the

corresponding areas on the right In the right midlung field the racing shows the pulsations of the right auricle and ventricle transmitted through an atelectatic area Autopsy showed extensive carcinomatous infiltration of the right main bronchus with extensive spread into the right upper lobe

✓ Electrokymographic findings were similar in different tumors (carcinoma sarcoma) when these affected a bronchus or a vessel The changes although not tumor specific became apparent even before alterations appeared in the standard chest x rays Electrokymographic changes were also seen with pulmonary infiltrations not due to tumors these changes were different from those seen with tumors

✓**Vagotomy in Hypertrophic Pulmonary Osteoarthropathy Associated with Bronchial Carcinoma** R L Huckstep and P E Bodkin[1] (Middlesex Hosp London) treated 2 patients with inoperable pulmonary carcinoma and severe hypertrophic pulmonary osteoarthropathy by vagotomy Both obtained immediate complete relief from disabling pain Associated edema and gynecomastia also disappeared Despite the progression of the disease pain and edema did not recur

The following points support the theory that hypertrophic pulmonary osteoarthropathy is primarily due to a nervous and not a chemical mechanism (1) If osteoarthropathy were caused by a chemical substance liberated by the tumor the most severe manifestations would probably be associated with tumors with extensive secondary deposits Local removal of a small tumor however may give remarkable and usually permanent relief from osteoarthropathy (2) The associated gynecomastia could be explained by the pulmonary autonomic systemic vascular reflex theory arteriovenous anastomoses opening up in the breast as in the limbs (3) Many lesions totally different in etiology and pathology produce the manifestations of hypertrophic pulmonary osteoarthropathy A common autonomic pathway could be postulated for most of these but would meet with many difficulties by a chemical or hormonal explanation

✓ In the authors patients simple division of the vagus produced relief from the pain and resolution of the edema although the pulmonary lesion was undisturbed

(1) La t 343 345 A g 16 1958

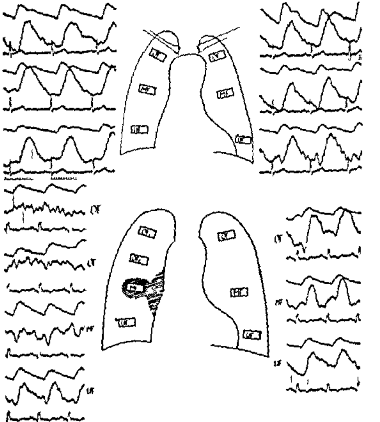


Fig 34 (top)—El t kym g ph find g d t scul d n ty h nges n periph al l ng fi ld f n rm l p son (l w t g ECG) d II m ddl t ng lect kymog m upp r t g a ot d p l)

Fig 35 (bott m)—El ct kym g m f p t t w th b n h g c nc ight ppe l b In ght upp fi ld (OF a d OFs) no hythm u at MF transm tt d u ul r m em nt I th lu g a th wer no as l r d ty h ng d m n t bl by l tr kym g ph y

(Court y of L n r J F itsch G b R ntg n t hl n 89 534-544 No mber 1958)

movements of the patient and from transmitted movements of the heart and large vessels However changes from interference can be easily differentiated from pathologic changes In all 200 patients with normal chest x rays the same tracing characteristics were found in the peripheral lung fields

Figure 35 shows the findings in a patient with bronchogenic cancer in the right upper lobe The electrokymogram revealed normal vascular pulsations in the left upper lung field but only atypical curves of minimal amplitude in the

epithelium had been observed to be associated with chronic inflammatory changes in the bronchial wall However the significant difference in incidence and extent of basal cell hyperplasia in patients with carcinoma of the lung and in smokers could not be explained on the basis of inflammation

Carcinoid Syndrome Produced by Metastasizing Bronchial Adenoma The carcinoid syndrome has now become an accepted entity The chemistry and physiology of 5 hydroxytryptamine the pharmacodynamic substance produced by metastatic intestinal carcinoid tumors has been studied extensively This substance (serotonin enteramine) has been recognized as a product of the chromaffin cells of the gastrointestinal tract the same cells from which the intestinal carcinoid tumor arises Richard R Pichel Warner and A Louis Southren[3] (New York) report 2 cases of functioning carcinoid tumor in which the primary tumor apparently arose in the lung rather than the gastrointestinal tract

Of the various manifestations of the functioning carcinoid syndrome those which occur most frequently are cyanotic flushes with hypotension diarrhea respiratory distress enlargement of the liver and increased urinary 5 hydroxyindoleacetic acid Cardiac changes usually occur late in the clinical course but sometimes may be absent The first patient had a pulmonic murmur and right sided heart failure but autopsy disclosed no pathologic changes in the right heart valves Except for peptic ulcer and arthritic changes which have been noted in less than half the reported cases this patient exhibited all the typical manifestations of a functioning carcinoid syndrome The second patient had all the main symptoms except wheezing during attacks and ulcer or arthritic complaints Right sided heart disease was clinically demonstrable and confirmed by special cardiac studies

Many of the symptoms of this syndrome are the direct result of excessive serotonin produced by the tumor No condition other than malignant carcinoid has been found to cause excessive urinary excretion of 5 hydroxyindoleacetic acid Hence a positive qualitative urine test will determine this metabolite as pathognomonic

Rauwolfia therapy produced some symptomatic improvement in the first patient other medication was ineffectual The second patient improved on promazine therapy

(3) Am J M d 24 903 914 J 1958

Multiple Primary Cancer of Lung was observed by C L N Robinson and C A Jackson (London) in 9 of 500 patients with bronchial carcinoma The criteria for diagnosing multiple primary tumors were macro and microscopic independence Macroscopic independence is easy to distinguish but the difficulty in accepting the duality of origin of primary pulmonary cancer on histologic grounds depends on whether pleomorphism can be excluded in serial sections of any one tumor All the patients were men aged 46 80 The two primary cancers presented simultaneously in 8 patients and in 1 the second developed 5 years after presumed cure of contralateral primary tumor by lobectomy In 4 the tumors were on the same side and in 5 in opposite lungs Adenocarcinoma was found in 1 patient subsequent to polygonal cell carcinoma and in 1 with oat cell carcinoma

Several writers have discussed the potential of bronchial epithelium to develop multicentric sites of origin of cancer Walter and Pryce described appearances in epithelium adjacent to the tumor similar to that seen in Bowen s disease of the skin They thought it probable that some squamous cell tumors started as intraepidermal carcinomas Auerbach and others made extensive microscopic studies of all grossly normal areas from the tracheobronchial tree in 54 patients who died of bronchial carcinoma They found separate areas of carcinoma in situ in 89% of the patients and early invasive carcinoma in 9% and suggested that carcinoma in situ was a stage before invasion However these changes have been noted as commonly in the trachea as in the *bronchi* but it has never been suggested that incidence of tracheal carcinoma is increasing

Hamilton and others compared by multiple slide technic the bronchi of nonsmokers smokers in whom lung cancer did not develop and patients (opposite lung) dying of lung carcinoma Five types of epithelial changes were seen basal cell hyperplasia stratification squamous and transitional metaplasia and intermediate change The commonest was basal cell hyperplasia which was more extensive and encountered in significantly more of the smokers lungs including those with carcinoma The other changes showed only slightly higher incidence in the groups mentioned Except in basal hyperplasia the changes described in bronchial

( ) J Thor Surg 36 166-173 Aug t 1958

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(3) Am J M d 24 03 914 J 1958

Pulmonary Alveolar Proteinosis was observed by Samuel H Rosen Benjamin Castleman Averill A Liebow Frank M Enzinger and Richard T N Hunt[4] in 27 patients *The first patient discovered to have this condition who was* followed for almost 5 years is described

Man 23 at age 19 had a productive cough and fever He recovered uneventfully but thereafter noted shortness of breath on exertion X rays demonstrated a cloud in the lungs Intermittently for 7 years he had driven sand and gravel trucks and made many deliveries to lumberyards Physical examination revealed no clubbing of



F g 36 (l ft) Cott ny nd fe th y d n it s pp re tly trat d bo t h *h a youth 19*

F g 37 *(r ght)* —O r 4 a 1 t r some f the ch g h w app t r lu t on C rt n ne of n as d d n ty ugg t pe tence f le on po bly n a fib ot tate

(Cou t y f Ros n S H *et al* N w E gland J Med 258 11 3 114? June 5 1958)

the fingers and no adenopathy The chest was clear and expanded normally Vital signs were normal Chest x rays revealed bilateral ill defined infiltrate extending from and obscuring both hili (Fig 36) Films of the hands were normal Laboratory data included hemoglobin of 15 5 Gm / 100 ml hematocrit of 44 mm and a white cell count of 9 600 Total protein was 6 7 Gm /100 ml A tuberculin test was negative Culture of sputum showed a few colonies of Hemophilus influenzae and Staphylococcus aureus

At thoracotomy the surface of the lung showed multiple flat rather dense infiltrations which were pale yellow measured 2-4 cm and extended u 1 cm of the pleural surface On section the fine pul

(4) New Engl d J Med 58 1123 1142 Ju 5 1958

monary architecture seemed preserved throughout the areas of infiltration Palpation of the hilus revealed lobulated thickening that was not visualized No growth occurred on Sabouraud s medium or blood agar to which material from the operative specimen was explanted No acid fast bacteria were seen

During the 5 year follow up the patient has been well except for bouts of chest colds that confined him to bed for 1 week every winter He has no shortness of breath or dyspnea Chest films still show the infiltrate although it is somewhat le s severe (Fig 37)

The lesions of pulmonary alveolar proteinosis consist of





F g 38 (l ft) —Hem t xyl e p pa t on (m 30) M t n l ppea mor h mogeneou th n w h PAS t n Al eol th n Not l ght lymphocyt nfil tion w ll f bron h l t et m os d p t a eo m t ial n l men
F g 39 (r ght) —Pe od d Sch ff pos mat ial (m 48) Not th l eola wall la p d ou d d ma se p senti ng m t f ell (Co rt y f Ro S H et l N w E gla d J Med 2 8 11 3 114 J 5 1958)

deposit of a PAS positive granular and floccular proteinaceous material rich in lipids within the lumens of the distal air spaces where little if any reaction is usually produced (Figs 38 and 39) This material is derived from granular transformation of proliferated septal cells and their subsequent sloughing and necrosis Acicular crystals and variable intensely staining laminated bodies believed to be cellular fragments were abundant in some fields in most patients Radiographically the appearance simulates that of pulmonary edema but the changes may persist for months or years they may clear remain more or less stationary or progress

Clinically the disease may or may not be heralded by febrile illness It is usually manifested by dyspnea often associated with cough that sometimes yields yellow sputum and by increased fatigability and weight loss Death may occur due to *progressive filling of alveoli or superimposed* fungous or bacterial infection which may be abetted by prolonged use of antibiotics and adrenocorticoids Corticoid therapy in most patients does not seem to affect the disease course and antibiotics appear indicated only in the presence of superimposed acute bacterial infections

Nothing is known of the cause of the condition Certain x ray and histologic similarities to pneumocystic infection have stimulated intensive but fruitless search for this parasite The homogeneity of the tissue response among the various patients and the clinical differences from pneumocystic pneumonitis suggest some other causative agent e g some recently introduced inhalant

► [This collaborative report is from the Central Laboratory for Pathologic Anatomy and Research Veterans Administration Armed Forces Institute of Pathology and the pathology departments of Harvard Medical School and Massachusetts General Hospital and Yale University School of Medicine These credits are mentioned because this bids fair to be one of the most important contributions of the past year in the field of pulmonary diseases Whether or not the condition proves to be an etiologic entity the collaborative approach to the description of what may be a new disease and the thorough manner in which the study was made give this report a character of outstanding interest and excellence —Ed]

Congenital Pulmonary Lymphangiectasis was observed by K M Laurence[5] (London) in 10 infants Five other cases have been reported in the literature The condition is not rare but unrecognized especially in its microscopic form In congenital cystic pulmonary lymphangiectasis the lungs are usually bulky and inelastic with pronounced lobulation Prominent subpleural lymphatic vessels form a dense network and usually subpleural cysts can be seen with the naked eye These may measure up to 3 mm in diameter and are transparent and glistening Histologically the cysts are situated mostly in the connective tissue under the pleura and in the interlobular septa though collections of smaller spaces can be found within the lobules They are often closely related to bronchi and blood vessels sometimes sharing a common wall

The spatial arrangement of the cystic spaces within the lung was investigated Serial sections 10 μ thick were cut

(5) J Cl Path 12 6 69 J y 1959

and the preparations projected onto cellulose acetate sheeting by a projector fitted with a microscope attachment Outlines of the spaces were drawn in India ink in consecutive sections in one area and in every fifth section in other but larger fields The tracings were superimposed accurately one on another after lightly coloring the lumina (Fig 40) From these it became evident that the spaces are part of an intricate network of intercommunicating channels The individual channels vary in width not only from each other but also



Fig 40—R ... t u t ... (20 ... l ect ... (10 μ th k ... with outl ... f ... y t p ... d w ... n l d ... k d l m ... lightly h d l ... Pl u ... and in ... blood ... } ... lightly ... d ... t d ... Lymph t ... p ... part f ... t ... u ... tw k f ... { (C rt y f La ... K M ... J Cl ... P th 12 6 69 J ... ry 1959)

in different parts of the same channel Thus a space only 15 μ in diameter may be in direct continuity with a cystic dilatation 2 mm in diameter The channels are constantly changing direction and may double back on themselves or take a spiral course In the sections examined none of the cysts appeared to be without a communication with the rest of the network and no true valves were found

The position of the cystic spaces in the normal distribution of lymphatics as described by Miller their close rela

tion to blood vessels and bronchi and their structures can leave little doubt that they *must be derived from lymphatic* vessels As the condition appears to be found only in stillborn and *newborn infants it can be assumed to be congenital The* only case reported in an older subject is likely to be one of *bronchial cystic disease with the cysts having the endothe* lium like lining referred to earlier

Pulmonary Cirrhosis In reviewing the history of this dis ease F Grosse Brockhoff[6] (Med Academy of Dusseldorf) *finds that it was first described by Rindfleisch in 1897* The lung changes consisted of shrinkage firm consistency a net *work of connective tissue scars* and cystic pea to cherry sized vesicles on the cut surface A year later Hansemann *recognized the changes as an independent disease and called* it reticular lymphangitis because of the characteristic *chronic interstitial connective tissue proliferations The sim* ilarity between pulmonary and liver cirrhosis was stressed by Meessen *in 1944 Histologic findings in Meessen s cases* included reticular perivascular and peribronchial scar for *mation with emphysema blebs bronchiolitis and secondary* pulmonary sclerosis No causative agents have been found

In 1935 Hamman and Rich *described a syndrome of dif* fuse interstitial pulmonary fibrosis with the following char *acteristics inflammation distinguished from ordinary pneu* monia by edema hemorrhage and few leukocytes thick *ening of the alveolar epithelial cells partial necrosis of the* alveolar and bronchial epithelium formation of hyaline *membrane lining the alveoli widening of the alveolar septa* by edema and fibrin deposits in the early stages and later *widening of the alveolar septa* by connective tissue prolif eration presence of eosinophil cells in the interstitium and absence of staining bacteria

It is believed that the so called Hamman Rich syndrome *is identical* with the previously described pulmonary cirrho sis Hamman and Rich called attention to the fact that onset may be acute and rapidly progress to death However the disease is usually chronic Present reports indicate that death may occur in 1 month to 20 years

► Recent clinical reports of cases characterized by pathologic criteria as Hamman Rich disease emphasize the chronicity of the condition in most patients *This is in contrast to the original clinical description of the syn* drome by Hamman and Rich who stressed the acute or fulminating course

(6) D tsch med W hnsch 83 677 681 Ap 18 1958

in most of their patients Grosse Brockhoff cites earlier descriptions of a disease which is similar if not identical to the condition known as the Hamman Rich syndrome At the same time he credits these authors with having been the first to describe the early stages of the syndrome and in having stimulated a new interest This historic note will particularly interest students of this type of diffuse interstitial pulmonary fibrosis —Ed]

Lung Changes in Acquired Heart Disease are of most value in mitral valve lesions and left heart failure according to Peter Kerley[7] (Westminster Hosp London) The size of the ventricles the size of the left auricle and valvular calcification often are fallacious Primary lung changes in mitral valve disease are distention of the veins distention of the lymphatics and distention and contraction of the arteries Secondary changes are hemosiderosis bone formation in the lungs pulmonary fibrosis secondary emphysema and atelectasis

In the normal x ray of the lungs the upper lobe veins are invisible or barely visible whereas the lower lobe veins especially on the right are easy to identify When the mitral valve area becomes narrowed the upper lobe veins stand out clearly Early upper lobe venous distention probably indicates generalized carditis If fibrous ankylosis of the valves and mitral incompetence results the distended upper lobe veins will gradually disappear unless left ventricular weakness comes into play If mitral stenosis is established the upper lobe veins remain distended and paradoxically the lower lobe veins become invisible

After venous pressure rises above 25 mm Hg (value of the plasma osmotic pressure) there is increased transudation of fluid and the pulmonary lymphatics become visible The intercommunicating lymphatics seen as the transverse lines at the bases are the first to appear but if an acute episode occurs the deep lymphatics also show up The latter appear bizarre being about 1 mm thick and running as long straight lines in haphazard fashion Engorgement of the deep lymphatics is usually transient whereas the intercommunicating ones vary little except with prolonged bed rest when they may become less conspicuous or disappear Similar linear or interstitial edema can occur in acute or chronic left ventricular failure and in some forms of malignant disease and pneumoconiosis but never to the same extent as in mitral disease In mitral disease the lines alone should

(7) Am J Roe tg 1 80 56 63 A g t 1958

never be accepted as an indication of pulmonary artery hy pertension

In minor mitral stenosis little or no alteration is ob served in the x rays of the pulmonary arteries In severe pul monary hypertension the main stem the two main branches and the second degree branches are enlarged whereas the peripheral branches are narrowed and tortuous Distended upper lobe veins contracted lower lobe veins and marked interstitial lines mean that mitral stenosis is dominant over mitral incompetence Distended upper lobe veins plus inter stitial lines and small peripheral arteries indicate predomi nant mitral stenosis with pulmonary hypertension Dis tended upper and lower lobe veins indicate low pulmonary pressure so that when the lower lobe veins are visible it is safe to assume low pressure Simon has graded the mitral lesion into six groups on these patterns

Hemosiderosis appears as a fine granular pattern like a first stage pneumoconiosis or as dense larger miliary opaci ties 1 2 mm in diameter Physiologically hemosiderin should be deposited only when the pH of the lungs is altered by severe venous congestion and it can disappear after val votomy Bone formation in the lungs in heart disease is al most conclusive of mitral stenosis

Exceptional complications of mitral stenosis are pulmo nary artery thrombosis and pulmonary vein thrombosis Thrombosis of a main artery can occur gradually It re ults in gross hypertranslucency of the affected lung and being unilateral or unilobar is easily distinguished from hyper tension

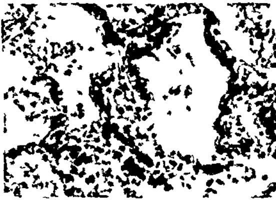
The x ray signs of left ventricular failure are distended upper lobe veins venous swelling and edematous glands making the hilar shadows big and ill defined slight inter stitial edema with transverse lines at the bases and occasion ally lamellar pleural effusions These signs are conspicuously absent in bronchitis or asthma In some patients some com bination of these signs appears before there is clinical evi dence of failure

Many patients are deemed inoperable because of chronic failure chronic basal infection honeycomb fibrosis and col lapse often in the right lower lobe

Fatal Pulmonary Changes during Medical Treatment of Malignant Hypertension were observed and reported by T

Hildeen A R Krogsgaard and Bj Vimtrup[8] (Copenhagen)
Woman 35 had blood pressure of 260/160 mm Hg ophthalmoscopy showed papilledema recent and old hemorrhages and cotton wool exudates and she had albuminuria Reserpine pentolinium and hydralazine were given by mouth but the blood pressure continued to fluctuate Reserpine was discontinued and hydralazine slowly increased to 400 mg /day The papilledema resolved and renal function was maintained About 4 months later severe edema and dyspnea developed Chest x ray showed severe *pulmonary congestion* She died 3 weeks later

Autopsy showed advanced arteriolar sclerosis in the kidneys Only the peripheral zones of the lungs contained air Microscopy showed gross increase in interstitial tissue (Fig 41) The alveolar



Fg 41—F b bl t p l f to d l k yt nd l mphocyt filt t n f t l eol septa d d f om 80 (Co rt y f H ld T t l Lan t 830-83 O t 18 19 8)

septa were thickened and contained tortuous dilated capillaries proliferating fibroblastic tissue and scattered masses of fibrinoid substance Only a few of the alveoli were obliterated but many were reduced to mere slits by dome shaped excrescences of fibroblastic tissue The alveolar epithelium was swollen and partly covered with *fibrin deposits*

Pneumonitis complicating the treatment of hypertension has been reported in *22* patients All but 1 had malignant hypertension and in all but the authors patient hexamethonium had been used *Hydralazine (Apresoline®)* had been given besides ganglion blocking agents to about half the patients in previously reported cases in none of these had the hypertension been well controlled The lung complication develops suddenly or gradually over a few weeks and

(8) Lancet 830 832 Oct 18 1958

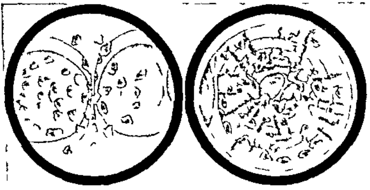
shows itself by increasing dyspnea Prognosis is bad all but 1 patient died The x rays show diffuse or nodular infiltration of both lungs starting from the hilar regions At autopsy by the naked eye examination appearance of the lungs may suggest simple congestion but microscopic examination *reveals the characteristic changes that involve the inter* alveolar septa It is probable that the earliest change is infiltration by lymphocytes and plasma cells and that these cells are later replaced by proliferating fibroblastic tissue A hyaline membrane may develop along the alveolar walls and if there is much exudation the microscopic picture may suggest uremia

Opinions differ about the cause Doniach and associates believe that repeated attacks of left sided heart failure with partial recovery under hexamethonium therapy were responsible the fluctuating blood pressure would thus be an important aggravating factor Perry and associates blame hexamethonium itself They described postmortem findings in three groups of patients those who died of malignant hypertension without treatment with hexamethonium those who had hexamethonium therapy and those who had mitral stenosis The lung changes which they called fibrinous pneumonitis were commonest in the second group and they had developed at much lower blood urea levels than in the first group In the mitral stenosis group few patients had pneumonitis

Amyloidosis of Lower Respiratory Tract was studied in 2 patients by C Barrington Prowse[9] (Royal Sussex County Hosp Brighton England) who also reviewed the reports on 16 patients and classified the total of 18 into three groups In group I consisting of 4 patients the amyloid material occurred in the lung only producing silent tumors found incidentally at autopsy after death from an unrelated cause All 3 patients in group II had an amyloid tumor involving a branch or branches of the bronchial tree and causing respiratory symptoms but the bronchial passages as a whole were free from amyloid deposits The 11 patients of group III were characterized by diffuse infiltration of the trachea and bronchial passages with amyloid material which was deposited under an intact mucosa in ridges folds plaques and mounds and caused intrinsic narrowing

(9) Thorax 13 308 3 0 Decembe 1958

Tumors in group I are clinically silent do not affect longev ity and need to be remembered only in differential diagno sis of other solitary tumor masses Those in group II may also be silent but even when the amyloid tumor involves a bronchus the resulting features do not differ from those of other solid tumors within the lungs or mediastinum Bron choscopy in this group is of value only to exclude com moner causes of bronchial obstruction unless the bronchial wall itself is infiltrated with amyloid and gives biopsy proof Thoracotomy is generally necessary to establish the diagno



Fg 4 —D w g f (l ft) d l ft l w lob b h (ght) w th t b nch t b h py (Co rt y f P w C B Th 13 308 3 0 Dec mbe 1958)

sis and offers the prospect of curative resection Radiother apy is probably useless and local removal of amyloid tissue of limited value and not without hazard By contrast the pa tients of group III have a clear clinical pattern and unique bronchoscopic (Fig 42) and pathologic features that may be considered as constituting a distinct clinicopathologic syn drome for which diffuse tracheobronchial amyloidosis would be a suitable name

In diffuse tracheobronchial amyloidosis the average age at onset of symptoms is 45 years men predominate Among the patients reviewed recurrent bronchitis hoarseness or loss of voice wheezing stridor and progressive effort dyspnea were all encountered singly or in combination for varying periods up to 40 years The four principal symptoms are cough dyspnea stridor and hoarseness *The physical signs* are those of associated bronchopulmonary infection and pul

monary collapse and consolidation On bronchoscopy the lesions are widely dispersed irregular in size and shape and diverse in color *In the subglottic region where the largest* deposits occur they may reach the size of a cherry and become pedunculated in the trachea smaller deposits are the rule The deposits are generally *greatest in the carina*

Fibrocystic Disease of Pancreas and Diabetes in Adult with Unusual Pulmonary Manifestations was observed by David M Caldwell and Delbert H McNamara[1] (Santa Barbara Gen l Hosp) Cystic fibrosis of the pancreas is predominantly a disease of infancy Though the cause is still unknown much progress has been made toward better understanding of the disease When the widespread involvement of all the mucous producing exocrine glands in the disease was described the term mucoviscidosis had been suggested because of the thickening of the mucus that occurs More recently it has been pointed out that both names are improper because the pancreas is usually but not always involved and the disease is not confined to the mucous producing exocrine glands In the light of present knowledge the term generalized exocrinopathy has been suggested as *more accurate*

Criteria that have been proposed for diagnosis of cystic fibrosis of the pancreas are pancreatic deficiency pulmonary changes excess chlorides in sweat and family history These criteria were met by the authors patient

Woman 24 had a history of cystic fibrosis of the pancreas from birth through childhood She also had severe diabetes mellitus At age 17 chest x rays showed no evidence of the disease *However 4 years* later extensive snowflake infiltrative shadows were seen in both lung fields

Hiatal Hernia with Gastric Occlusion and Intrathoracic Perforation of Gastric Ulcer on Greater Curvature is reported by Seymour Fiske Ochsner and Alton Ochsner[2] (Ochsner Clinic)

Woman 79 *was hospitalized because of severe nausea and hema*temesis She had a known hiatal hernia Gastrointestinal x ray studies showed that the stomach was rotated as well as inverted in a large herniated pouch and obstruction was complete in the antral portion above the *diaphragm (Fig 43) The gastric wall was ir*regular vaguely defined marginal outpocketing suggested a possible ulcer crater A few days later sudden ... re steady pain developed in the left upper abdominal quadrant e ... ing to the back and shoul

(1) Calif M d 89 280-84 O t be
(2) Am J D g 96 56 564 Oct be 1958

der The pain was aggravated by breathing At surgery much fluid was found in the right pleural cavity as a result of perforation of the gastric ulcer through the hernial sac The gastric ulcer was on the greater curvature of the stomach The ulcer bearing segment was resected the hernial sac excised the stomach mobilized and replaced





F g 43 (l ft) —X y 2 h ft g t f b m how g b m sophagu d f l f t m h N b m p d f m f d f t m h t th t port th t l bo d ph gm

F g 44 (ght) —P t p rat g t t t l x y h w g ll f t ma h b l w diaph gm d d fect g t t f tom h es lt f w ig ect n f lc

(Court sy f Och S F d O h A Am J S g 96 56 564 Oct be 1958)

into the abdomen and the diaphragmatic hernia repaired On pathologic study the gastric ulcer proved benign measuring 1 cm in diameter

Postoperative recovery (Fig 44) was prompt complicated only by the pleuritis and apparently moderate atelectasis and pneumonitis that developed in the right lung and subsided within 1 week

A small symptomless herniation probably should be considered as generally unimportant Minor symptoms may be improved by diet and reduction of the obesity that is usually present Surgical repair should be considered if hiatal hernia is associated with definite symptoms such as pain or troublesome regurgitation if successive x ray studies show that the herniation is enlarging if there is ulceration in the herniated stomach if there is unexplained hemorrhage or if there is evidence of obstructive changes

THE BLOOD *and* BLOOD-FORMING ORGANS

WILLIAM B CASTLE MD

PART III

THE BLOOD AND BLOOD FORMING ORGANS

GENERAL TECHNICS AND TOPICS

Quantitative Measurement of Erythrocytic and Granulocytic Cells of Marrow and Blood was made by Dennis M Donohue Robert H Reiff Mary Lu Hanson Yvonne Betson and Clement A Finch[1] (Univ of Washington) who related *numerically (1) the erythroid marrow to the circulating red* cell mass and (2) the granulocytic marrow to the circulating granulocytic leukocytes in rats rabbits monkeys and man The method uses the erythroid tag Fe^{59} to relate the cells in an aliquot of marrow to the total marrow as proposed by Suit In man marrow was obtained from rib sections removed at thoracotomy from male patients with controlled tuberculosis

The number of nucleated red cells is comparable in 3 of the 4 species when expressed as cells/kg body weight the rat had $5\ 5 \times 10^9$ the rabbit 5 8 and man 5 4 whereas the monkey had 9 2 In these 4 species the combined reticulocytes of marrow and blood were 14 5 16 4 8 95 and 11×10^9 cells/kg respectively Of this total compartment the percentage in the marrow was 42 29 65 and 56 Average figures for red cells were 493×10^9 370 309 and 380 respectively Circulating granulocytes in rats rabbits monkey and man averaged 0 17 0 24 0 44 and $0\ 30 \times 10^9$ Total marrow granulocyte forms were 6 7 4 8 15 4 and $11\ 4 \times 10^9$

Various experimental approaches have been used to estimate the number of marrow precursors of the circulating blood elements (table) Total hemopoietic tissue has been reported to range from 12 to 49×10^9 marrow cells/kg nucleated red cells from 3 to 22×10^9 cells/kg and granulocytes from 4 8 to 27×10^9 cells/kg The only fraction of erythroid cells capable of cell division is within their nucleated cell pop

(1) J Cl I t 37 1571 15 6 N mb 1958

H^3 thymidine combined with high resolution autoradiographic technics permits some insight into the development of specific cell lineages

In attempting to establish cultures from leukemic blood for study with H^3 thymidine using Osgood's technic it was noted that 1 hour of incubation of bone marrow or blood cells was sufficient to indicate presence of desoxyribonucleic acid synthesis in various cell type The procedure promised to provide information on the proliferative capacity of differ



Fig 45 —B m row 5 m 1 pe so and p t ent w th n pla t d ea *A* norm l m w t bel g of se ral mmat type *B* l bel d my l po t cell *C* label d rythropo et c ll ed d f om 800 (Court f Bond V P *et al* Act h mat 21 1 1959)

ent cell types and its simplicity offered the opportunity for single or serial studies in many patients This approach of in vitro labeling was used by the authors to investigate the proliferative potential of bone marrow peripheral blood cells and other tissues of human beings with normal and abnormal hemopoiesis Label was demonstrated not only in immature cell types as might be expected but also in cells considered previously from their morphology to be incapable of proliferation

In normal bone marrow labeling was noted at 1 hour in all cell lineages and in cells variously referred to as retic ulum stem stroma etc Erythropoietic cells were labeled as far as the polychromatic normoblast the myeloid series was labeled to the myelocyte state (Fig 45) Leukemia cells in the bone marrow and peripheral blood of patients with acute or chronic myelocytic leukemia incorpo

ulation In the granulocyte precursors it is likely that only myelocytes and their precursors are capable of cell division

Since the number of red cells produced may be calculated from the number and life span of circulating red cells the doubling time of the nucleated red cell fraction may be es timated Red cell turnover is assumed to be 1%/day in man and monkey and 2%/day in rat and rabbit Figures for dou bling time of nucleated red cells would be 0 56 day in rats 0 76 in rabbits 2 43 in monkeys and 1 7 in man These calcu lations are approximate and it is assumed that no great

QUANTITATIVE ESTIMATES OF HEMATOPOIETIC TISSUE OF MARROW

A th	Spec	E yth d mar w (ll /Kg X10⁹)	G locytic marr w (cell /Kg X10⁹)
Kindred (6)	Rat	10 0	14 6
Yoffey (8)	Guinea p g	6 7	9 6
Osgood (9)	Man	8 6	25 7
Fair (10)	Rat	22 0	27 0
	Dog	6 7	11 5
	Man	3 4	8 3
Suit (14)	Man	4 6	
Present eport	Rat	5 6	6 7
	Rabbit	5 8	4 8
	Monkey	9 2	15 4
	Man	5 0	11 4

Ex lues of adult gra ul yt

discrepancy exists between total and effective erythropoie sis Man appears to have a large reserve of mature granu locytes in the marrow—8 times the amount in circulation Including both granulocytes and stab forms the marrow re serves are about 20 times those in circulation Leukocytic production rates and survival are unknown but the figures indicate the presence of an appreciable pool of leukocytes in the marrow

Proliferative Potentials of Bone Marrow and Blood Cells Studied by In Vitro Uptake of H^3 Thymidine are described by V P Bond T M Fliedner E P Cronkite J R Rubini G Brecher and P K Schork (Brookhaven Nat l Lab Up ton N Y) Tritium labeled thymidine (H^3 thymidine) has provided a potentially useful approach for study of the dy namics of rapidly proliferating tissues because thymidine is incorporated solely into desoxyribonucleic acid Serial sampling of the tissues after injection and incorporation of

(2) Act ha mat. 21 1 15 1959

H^3 thymidine combined with high resolution autoradiographic technics permits some insight into the development of specific cell lineages

In attempting to establish cultures from leukemic blood for study with H^3 thymidine using Osgood s technic it was noted that 1 hour of incubation of bone marrow or blood cells was sufficient to indicate presence of desoxyribonucleic acid synthesis in various cell types The procedure promised to provide information on the proliferative capacity of differ



Fg 45 —B m w f rm l per on d p t t w th on eopl t d *A* m l m w l bel g f l mm t typ *B* l b l d my l poi t ll *C* label d yth po t ll d d f om ×800 (Court y f B d V P *t l* Act h m t 21 1 15 1959)

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	Man	3 4	8 3
Su t (14)	Man	4 6	
P esent repo t	Rat	5 6	6 7
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(2) Acta ha mat 21 1 15 1959

Densely labeled telophases of both myeloid and erythroid series were found in marrow by 4 hours (Fig 46) When the number of positive cells was computed in terms of normalized distribution of various cell types there was a rapid increase with time Since part of the label passes to the daughter cells of a labeled progenitor several mitoses may be required depending on degree of initial incorporation before the label is no longer detectable above background The number of positive cells began to decrease by 48 hours owing to dilution of the label by mitosis and possibly the beginning of release of labeled cells from marrow Turnover

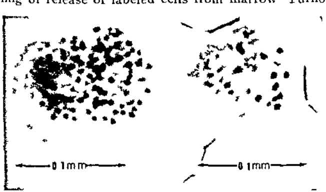


Fig 46—L ft d oa tog ph f my l yt ma w 4 h ft j t n f t t t d thym d R ght gm t d eut ph l blood 4 days ft ject n (Cou f y f Mal y M \ d P tt H M P oc Soc E p B l & M d 8 801 803 A g Sept 1958)

time of proliferating myeloid elements can be approximated from rate of increase of positive cells and is of the order of 15 hours Consideration of time relationships between thymidine administration and increment in labeled mitoses as well as the decrement in grain counts should provide a more complete picture of the life cycle of various proliferating cells

Distribution of labeled myeloid cells progressed in an orderly manner from the less to the more differentiated forms There was a comparable progression of the label in nucleated erythrocytes Only 1 3% of lymphocytes were labeled in marrow samples from 12 hour to 5 days after injection of tritiated thymidine Labeled metamyelocytes appeared in bone marrow within 12 24 hours and band cells within 24 36 hours Tagged neutrophils (segmented) could be detected in aspirated marrow within 2 3 days and in peripheral blood

rated label avidly The small typical leukemia cell of chronic lymphocytic leukemia did not label at all Less than 3% of the myeloma cells in patients with multiple myeloma incorporated thymidine Most striking was the finding of a few labeled large mononuclear cells of different morphologic types in the peripheral blood of normal human beings and increase in the number of morphologically identical cells in the blood of patients with infection and infectious mononucleosis The labeling indicates active desoxyribonucleic acid synthesis and thus these cells presumably are capable of division These cells may represent a mobile pool of primitive progenitor cells and are multipotential in their function

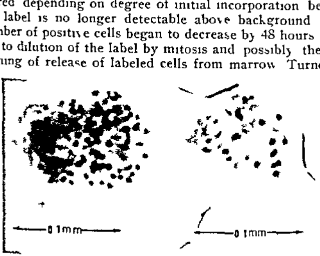
Parallel in vivo studies with bone marrow indicate that the in vitro results within the first hour of incubation are identical with those obtained in vivo when marrow is removed at 1 hour after injection of thymidine It may therefore be presumed that the in vitro results adequately reflect *the in vivo capacity of various cell types for desoxyribonu*cleic acid synthesis at the time of sampling

Neutrophil Life Cycle with Tritiated Thymidine is discussed by Mary A Maloney and Harvey M Patt[3] (Argonne Nat l Lab Lemont Ill) Patterns of neutrophil balance can be brought into sharper focus than heretofore possible by *high resolution radioautography with tritium labeled thymi*dine A rather precise localization may be achieved with this labeled nucleoside because of its specific incorporation into desoxyribonucleic acid and the short range of tritium beta particles The labeled exogenous precursor is apparently available only for a brief period after administration which is an added advantage *Neutrophilic leukocytes are part of a* highly labile renewal system and the kinetics of their development in vivo can be determined from temporal changes in degree of labeling and distribution of the various cells in developmental sequence

The pattern of neutrophilic granulocyte development was studied *in 2 dogs The tritium label appeared first in im*mature cells which ordinarily contribute to renewal of myeloid and erythroid populations by mitosis About 15% of myelocytes and 20% of erythroblasts in marrow aspirates were labeled within 2 hours after injection of tritiated thymidine Labeled lymphocytes were not seen at this time

(3) *Proc Soc Exper Biol & Med* 98 801 803 Aug Sept 1958

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Fg 46—Left d t g ph f my locyt m ow 4 h ft j ct f tnt t d thym d R ght gment d eut ph l n blood 4 day ft njec (C tesy f M l M A nd P tt H M P oc Soc E pe B l & M d 8 801 803 A g S p 19 8)

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by 3-4 days The first labeled neutrophils may be released from marrow somewhat earlier without detection in circulation owing to their rapid dilution in the large extravascular pool

Dependence of Bone Marrow Cells on Liver for Purine Supply was studied experimentally by L G Lajtha (Oxford) and J R Vane[4] (London) by measuring the amount of C^{14} formate incorporated into the desoxyribonucleic acid bases of bone marrow cells in control and hepatectomized rabbits Little difference was found between the ratios of specific activity of thymine and adenine in the nonanesthetized control anesthetized and nephrectomized rabbits The mean ratio was 1 05 indicating a similar degree of incorporation of C^{14} formate into both the purines and the thymine of the desoxyribonucleic acid in bone marrow cells in vivo

In the hepatectomized rabbits incorporation of C^{14} formate into the adenine of bone marrow cells was substantially depressed thus raising the thymine adenine ratio to 27 A similar thymine adenine ratio was found in the rabbit in which the intestine was removed with arrest of the portal circulation In the rabbit in which portal blood flow was restored after removal of the intestines the thymine adenine ratio was 3 17 indicating that C^{14} formate was efficiently utilized in formation of bone marrow adenine

The experiments show that the *de novo* synthesis of purines in bone marrow cells is greatly reduced by hepatectomy It is unaffected by nephrectomy or removal of the gastrointestinal tract as long as portal blood flow is maintained Three interpretations are suggested (1) In animals the liver provides an enzyme with which the bone marrow cells can synthesize purines (2) The liver provides an advanced precursor which the bone marrow cells can transform into purines (3) The liver supplies pre formed purines which are taken up by bone marrow cells

If the liver provides an enzyme it must have a very short life for it was found that even 5 10 minutes after hepatectomy the bone marrow cells could not utilize C^{14} formate efficiently for synthesis of purines If the liver supplies an advanced precursor to the bone marrow then bone marrow cells in vitro should be able to utilize 5 amino-4 imidazole carboxamide or its riboside (one of the last steps in the pu

(4) Nat London 182 191 19 J ly 19 1958

rine pathway) It has recently been shown that these sub stances are utilized inefficiently for synthesi of purines compared with the uptake of C^{14} adenine into purines or of C^{14} formate into thymine This leaves the third possibility which is further supported by the observations that although bone marrow cells in vitro have a limited capacity for purine synthesis they can utilize pre formed adenine efficiently

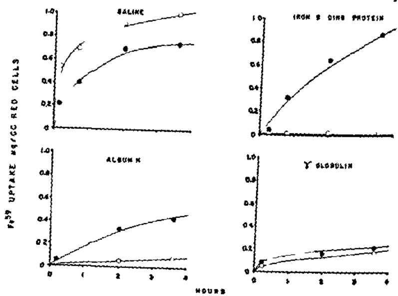
Transfer of Iron from Serum Iron Binding Protein to Human Reticulocytes The metabolism of iron involves a series of compounds that restrict iron to undissociated forms When absorbed by gut mucosal cells iron is enveloped within ferritin molecules In the presence of reducing agents ferritin iron is released to the surfaces of ferritin molecules to become bound by a specialized transport protein of the plasma This iron binding protein acts as a betaı globulin by electrophoresis but resembles albumin chemically Each molecule of iron binding protein (IBP) from human or other mammalian species or from egg white (conalbumin) binds two iron atoms to form a colored complex Iron thus bound is ferric and is tightly chelated in complexes that apparently contain three phenolic groups and one bicarbonate ion At physiologic pH and bicarbonate concentrations the iron IBP complex is extremely stable However iron is trans ferred from IBP to immature red cells and incorporated into hem

James H Jandl John I Inman Richard L Simmons and David W Allen[5] (Boston) found that iron transfer depends on the degree of saturation of IBI and that IBP and the iron binding receptors on the reticulocyte membrane com pete for the iron Free iron as $Fe^{59}Cl_3$ was bound equally by mature and immature red cells but iron bound to IBP (Fe^{59} IBP) was taken up almost exclusively by immature red cells (Fig 47) Uptake of Fe^{59} from the Fe^{59} IBP was in direct proportion to the reticulocyte concentration The cellular receptors on the reticulocyte membrane could be de stroyed experimentally by proteolytic enzymes Iron appears to be directly transferred to these receptors without existing in free form Once bound to reticulocyte membranes iron is not exchangeable with free iron and cannot be eluted with high concentrations of IBP or ethylenediamine tetra acetic acid

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(5) J Cl I t 38 (pt 1) 161 185 J y 1959

The transfer of IBP iron to immature red cells requires energy. It is accelerated by glucose and oxygen and is diminished or blocked by low concentrations of metabolic inhibitors, by nonphysiologic temperatures and by hemolysis. Iron uptake is not primarily linked to heme synthesis. Incorporation into heme by reticulocytes could be blocked by



F g 47 – Influ f p t n b d g n t ptak f n by mm t a d m t d cell F Cl w dded t l lb m n b d g p t n d γ gl b l s l t Aft l h u t oom tempe at th m tu w ncubated f 4 h u w th w h d u pen n f d ll nt ng 31 f mm tu ed ll (t c locyte) f m p t t w th q d h m lyt c m d w th h d p n f n rm l d lt d lls nly 0 3 f wh h w t l yt Upt k f F by w h d ell w th mea u d t t rv l N te trik g sel t ty w th wh h mmatu ed ll (l d l) mp d t d lt ed ll (p l) took up F f m onl nd g f t n (C urt f J ndl J H *et al* J Cl I t 38 (p 1) 161 18 J ua y 1959)

appropriate concentrations of lead but iron continued to be transferred thus causing pile up of iron on cell membranes

Unlike reticulocytes whose uptake of iron reaches a plateau when IBP is 20-30% saturated with iron rat liver slices take up iron in appreciable amounts only at high IBP saturations above 60% This transfer does not require metabolic energy and iron accumulated by liver slices can be eluted with unsaturated IBP suggesting a homeostatic mechanism for controlling the serum iron level

Free iron is bound equally by mature and immature red cells but free cobalt is more avidly bound by the immature cells Trivalent cobalt as does iron forms colored chelates with purified IBP and is bound by IBP of whole plasma Co balt bound to IBP can to limited extent be transferred pref erentially to reticulocytes However cobalt and IBP prob ably do not combine physiologically and this combination probably is not involved in cobalt polycythemia

Participation of Reticulocyte Microsomes in Incorporation of Iron into Hemoglobin Immature rabbit erythrocytes (reticulocytes) have been found to be involved in formation of hemoglobin This process has been measured directly by determining increase in hemoglobin or through incorpora tion of amino acids into globin glycine or iron into heme Following the kinetic evidence that the micro omes of intact reticulocytes particip ite in globin formation M Rabinovitz and M E Olson[6] (Univ of California) studied the steps of this synthesis with fractions of lysed rabbit reticulocytes prepared in the ultracentrifuge

Incorporation of iron required presence of both the micro some and soluble fractions and microsomes that were boiled did not show this incorporation Besides iron incorporation into hemoglobin an extensive incorporation of iron oc curred within the microsome itself This was also completely dependent on presence of the soluble extract The nature of the binding of this microsomal iron is not clear but it ap pears to be a hemoglobin precursor The results further sug gest that release of this precursor from the microsomes is stimulated by the energy source adenosine triphosphate and phosphoglycerate

These observations do not appear to be in accord with re cent suggestions by Eriksen who incubated intact rabbit reticulocytes with acetate $2C^{14}$ and found that labeled mi crosomal heme had the same specific activity as that in the soluble protein fraction He suggested that this eliminated the possibility that microsomal heme was a precursor of he moglobin The authors similarly found that heme protein removed from the microsomal ribonucleoprotein with de soxycholate had the same specific activity as that of the soluble protein after incubation of intact reticulocytes for short periods with C^{14} leucine It seems highly probable

(6) N t Lo d 181 1665 16 J 14 1958

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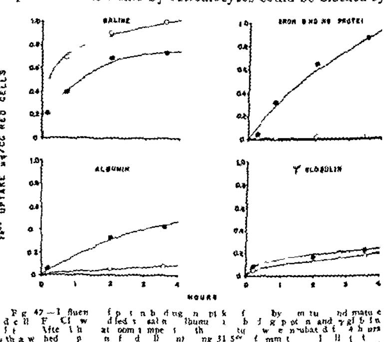


Fig 47.—I fluen[illegible] by [illegible] and matu[illegible] [illegible] saline [illegible] and γ gl[illegible] [illegible] [illegible] 31 5% [illegible] 0 3% [illegible] Fe by washed cells was then measu[illegible] [illegible] took up [illegible] (C[illegible] J Clin In[illegible] 38 [illegible] 161 185 [illegible] 195[illegible])

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amount of HbA which can be detected by starch block electrophoresis In thalassemia minor HbA is increased In thalassemia major the HbF content is much increased

The abnormal hemoglobins are transmitted like single dominant genes The genes of HbS and HbC and probably of most of the other abnormal hemoglobins too are alleles of the gene producing HbA Heterozygous carriers have HbA plus abnormal Hb in their blood Homozygous individuals have only the abnormal Hb no HbA There exist also doubly heterozygous individuals their blood contains two abnormal hemoglobins (e g HbS plus HbC) no HbA Individuals homozygous for HbS or HbC have a hemolytic anemia as do heterozygotes with both HbS and HbC The disease is most severe in the case of homozygous HbS (sickle cell anemia) In individuals homozygous for HbE D or G signs of sickness are mild or absent Heterozygous carriers with few exceptions are healthy from a clinical and hematologic viewpoint The abnormal hemoglobins therefore do not have a pathologic significance a priori on the contrary HbS seems to augment the resistance against malaria When the genes for both an abnormal hemoglobin and thalassemia are present in an individual not only the manifest signs of the disease are increased but also the content of the abnormal Hb in the blood [7]

Mechanism of Release of Ferritin Iron in Vivo by Xanthine Oxidase was investigated by A Mazur S Green A Saha and A Carleton[8] (New York) Studies of the biochemical mechanism for the release of iron from hepatic ferritin stores have revealed participation of the enzyme xanthine oxidase During this reaction between the enzyme and ferritin iron some of the iron in the ferric state is reduced to the ferrous form and can be removed from the protein in presence of iron binding agents such as a a dipyridyl or the plasma iron binding globulin siderophilin Evidence for participation of this enzyme in release of ferritin iron is based mostly on in vitro studies with rat liver slices subjected to lowered oxygen tension Such tissue slices accumulate ferrous ferritin and high levels of hypoxanthine and xanthine substrates for xanthine oxidase as well as uric acid their oxidation product Indirect evidence also implicates this mechanism in release of ferritin iron to plasma in

(8) J Cl I t 37 1809 1817 Dec mbe 1958

therefore that nearly all the heme protein on the micro somes becomes associated with these particles during iso lation and may obscure the presence of a smaller precursor fraction

The results support the earlier observations of Walsh and associates that the particulate matter of intact human reticulocytes incorporates iron and suggest that this process is associated with synthesis of hemoglobin

► [This is a valuable biologic simplification utilizing a cell free system capable of synthesizing hemoglobin Schweet *et al* (Proc Nat Acad Sc 44 1029 1958) have successfully used essentially the same technic in dem onstrating the incorporation of C^{14} labeled amino acids into hemoglobin in the proportions normally present—Ed]

Hemoglobin Anomalies are discussed by K Betke[7] (Univ of Freiburg) Three types of hemoglobin exist during hu man development embryonic or primitive hemoglobin (HbP) fetal hemoglobin (HbF) and adult hemoglobin (HbA) Their appearance is correlated to the mesoblastic hepatic and myeloid periods of blood formation respectively but there is no topographic correlation between the places of hemopoiesis and these hemoglobins In certain congenital and sometimes acquired blood diseases HbF may appear again during postnatal life

Besides the physiologic hemoglobins there exist several abnormal hemoglobins which appear along with or in place of HbA postnatally The best known is the sickle cell hemo globin (HbS) Further there are hemoglobins C D E G H I J K L M and others not yet definitely characterized These hemoglobins are functionally active without defect except for HbM which in vivo partially changes into methe moglobin probably by an increased spontaneous oxidation rate Hemoglobin H is almost twice as sensitive to oxidating agents such as nitrite as HbA

Concerning the content of amino acids only HbF and HbH are known to differ markedly from HbA Ingram has shown that both HbS and HbC have one different amino acid out of 300 in a half molecule as compared with HbA Because of their different physicochemical behavior the ab normal hemoglobins are easy to identify using the methods of denaturation by alkali paper electrophoresis chromatog raphy on cation exchange resins and solubility tests

Normal blood of adults contains besides HbA a small

(7) S h u med W h sch 88 1005 1010 Oct 11 1958

cells in a field of adult cell erythrocyte ghosts Arbitrarily each smear was scanned for 2 minutes under low power

When 3 adults were given 3 5 and 15 ml compatible placental blood intravenously the fetal cells were demonstrated in the expected concentration in smears of their blood In the adult receiving 15 ml the fetal cells were still demonstrable 6 weeks after infusion

The blood of 90 donors (men and nonpregnant women) was examined No fetal cells were found The blood of 42

RESULTS OF EXAMINATION OF MATERNAL BLOOD

N E amin d (M ut Sc)	N F al C s B	E m M Am al C of Fe (m)
33	0	0 0
2	1	0 1
3	2	0 2 0 3
3	3-4	0 4 0 7
1	16	2 0 3 0

mothers selected at random without reference to the blood groups of mother and child was examined on the 2d to 6th day post partum (table) The finding of fetal cells in 11 of 42 (21%) postpartum women suggests that placental passage of fetal blood is common This method has the advantage of not being dependent on the blood groups of the mother or fetus

Rapid Method for Estimation of Total Leukocyte Count has been devised by Naomi R Benjamin[1] (Walter Reed Army Inst of Res) In the event of atomic warfare one problem will be to identify those persons whose radiation injury is severe enough to require medical care The leukocyte count is a fairly good index of the dose of atomic radiation received and is the best screening procedure available However cleaning and loading of pipets and counting chambers requires about 10 minutes of a technician s time The method described eliminates the need for pipets and counting chambers

METHOD —The head of a straight pin i immersed in blood so a small drop adheres to the rounded surface of the pinhead which is immediately touched to the surface of a microscope slide to form a small round dot This is repeated two or three times The drops are smoothly dried by placing the slides over an electric light bulb The slide is immersed for 5 10 minutes in staining solution containing 0 02% (w/v) in tap water solution of formalin (5% v/v) or 1 cc Giemsa solution in 50 cc tap water formalin solution The water leaches the hemoglobin out of the red cells the formalin fixes

(1) Blood 13 677 693 J ly 1958

the intact animal as a result of liver hypoxia after extensive blood loss plasma iron and uric acid values in dogs have been found to increase considerably

The authors confirmed release of ferritin iron in the liver to the plasma after reduction by xanthine oxidase in intact guinea pigs rabbits and dogs Administration of xanthine oxidase substrates nucleotides or nucleosides which can be converted to such substrates by the animal leads to increase in plasma iron levels Inhibition studies in presence of excess substrate indicate that reduction of ferritin iron by reduced xanthine oxidase involves a site on the enzyme different *from that which reacts with molecular oxygen or methyl*ene blue The authors suggest that the site of ferritin iron reduction is associated with the nonheme iron of the enzyme and occurs by direct electron transfer

The physiologic stimulus which results in accelerated release of iron from hepatic ferritin stores to plasma is tissue hypoxia This produces an increase in level of xanthine oxidase substrates and a consequent reduction and release of ferritin iron to plasma Since the result of lowered oxygen tension is a stimulation of erythrocyte synthesis and thus of iron incorporation into hemoglobin the ferritin xanthine oxidase system constitutes part of a homeostatic mechanism for regulation of the level of iron in the circulation

Fetal Erythrocytes in Maternal Circulation were studied by Alvin Zipursky Alan Hull F D White and L G Israels[9] (Univ of Manitoba) Kleihauer *et al* reported that the hemoglobin of adult red cells in a fixed smear was readily eluted by an acid phosphate buffer whereas the hemoglobin of fetal cells was not The authors applied this observation to detect small numbers of fetal cells in the blood of newly delivered women

Method—Venous blood was collected with ammonium potassium oxalate as anticoagulant and diluted 1 3 with normal saline Smears were made of this suspension dried and fixed in absolute ethyl alcohol for 2 minutes Next the slides were washed for 90 second in citrate phosphate buffer (0 16 K_2HPO_4 and 0 18M citric acid pH 3 4 3 6 at 37 C) They were stained with May Grunwald stain and washed until practically *no stain was visible to the naked eye* After drying they were *examined microscopically under low power* In vitro mixtures of fetal and adult blood were made and smears prepared as described Fetal cells appeared as pink staining refractile

(9) Lancet 1 451-45 Feb 28 1959

material was carried out without premedication or anesthesia Once the needle was in place the patient experienced little or no discom fort Five cc of appropriate iodized oil was drawn into a syringe through a clean sterile 20 gauge needle With the lymph node firmly held between thumb and forefinger the needle was introduced di rectly into the center of the node The most suitable agent for the e studies proved to be Ethiodol* (purified iodized ethyl ester of poppy seed oil each cc of which contains 37% by weight of iodine)

It was found that the prior injection of hyaluronidase (spreading factor) not only enhanced the ease with which an injection could be carried out but facilitated the spread of the contrast substance to ad jacent lymph nodes An injection of 75 150 turbidity reducing unit



Fig 49—S l films t 15 m t t t val n w m ged 77 w th d gnos s f lymphosar om sh w sequence of fill g aft t n of gu l lymph od (Courtesy of Zhe tl N a d Sh b om E Rad ol gy 1 0 08 N embe 1958)

was given with a separate syringe This syringe was then detached while the needle was left in place and a syringe containing the iodized oil was attached to the same needle The Ethiodol* was injected at the rate of about 1 cc / 5 minute interval During this procedure re peated fluoroscopic observations were made and spot films taken (Fig 49) On completion routine x rays were made at 15 minute in tervals At present x rays are taken at completion of the injection and again in 1 2 hours and a repeat film is made 24 hours later The total amount of contrast medium injected ranged between 2 and 8 cc depending on size of the lymph node ease of injection and spread of contrast

This procedure makes it possible to visualize para aortic nodes by means of injection of iodized oil into the inguinal and femoral areas Furthermore it yields considerable in formation concerning the normal course of lymphatic chan nels It appears for example that there is a direct communi cation of the axillary nodes with the subclavian vein on that

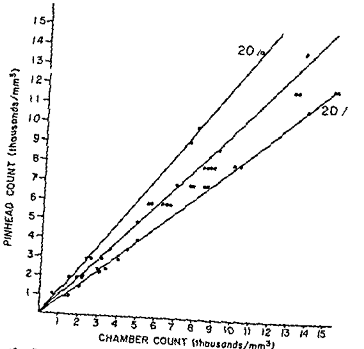


Fig 48 —C po den e betu n ch mber u t f l uk cyt and t m t s by p he d m th l on 84 on ecut t f by 3 te hn c a Count we e don th h ld du g 195 e e f w apon t t n he da p gs exp d t at m at at A small kn f w d wa m d n sk n of r to obta blood (Co rtesy of B j m n N R Blood 13 677 683 July 1958)

the drop and the leukocytes take up the stain during the immersion The slide is examined under low power (×25) visualizing the entire drop and the microscope field is compared with photographs of standard preparations

When compared with routine chamber counts (Fig 48) the pinhead method is accurate It can be used to screen leukocyte counts and a standard chamber count reserved for any blood that appears abnormal or even questionable The new method requires 60-90 seconds each when many counts are done

Contrast Visualization of Lymph Nodes discussed by Norman Zheutlin and Edward Shanbrom (City of Hope Med Center Duarte Calif) was carried out in 35 instances in 20 patients without untoward effects

METHOD—The skin overlying an accessible lymph node was cleansed with alcohol As in venipuncture injection of the radiopaque

(2) R d l gy 71 70 70 November 1958

normal Before the present examination 5 children bled after a surgical procedure 3 after circumcision and 2 after tonsillectomy

These results demonstrate the false positive and false negative reactions which can be obtained in the routine bleeding and clotting tests A normal result in no way assures a normal coagulation status in the patient Carefully taken family and past histories and adequate physical examinations as well as examinations of peripheral blood smears are far more informative and effective screening procedures If the history or physical findings are sufficiently suggestive of hemorrhagic disease a complete battery of coagulation tests should be done because these may be required to establish the nature of the hemorrhagic disorder

Studies on In Vivo Survival of Glycerolized and Frozen Human Red Blood Cells are presented by James L Tullis Melvin M Ketchel Hugh M Pyle Robert B Pennell John G Gibson II Robert J Tinch and Shirley G Driscoll[4] (Boston) The prolonged extension of red blood cell viability by low temperature technics could prove revolutionary to standard blood banking methods Blood was collected from healthy human donors by gravity flow into plastic bags containing anticoagulant acid citrate dextrose (ACD) solution and then connected to the red blood cell plasma separation bowl of a Cohn centrifuge After separation of the plasma a series of solutions was introduced which raised the glycerol concentration in the red blood cells from 0 to 50% over 45 minutes The cells were then transferred to an attached bag and the temperature was reduced to —80 C in about 7 hours After storage individual units of blood were thawed by immersion in a 37-40 C water bath for an average of 12 minutes and deglycerolized in the Cohn fractionator a technic essentially the reverse of the initial processing

Ninety four units of blood were collected glycerolized stored frozen deglycerolized stored at 4 C and then administered to selected recipients 33 were labeled with Cr^{51} before final transfusion No unfavorable reactions were observed after use of untagged units even though some recipients had well documented febrile respon es to ordinary banked blood both before and after transfusion of frozen

(4) J A M A 168 399 404 S pt 27 1958

side as iodized oil could be seen entering the subclavian vessels in several different points along its course This confirmed the finding of other investigators that there is considerable variation in the arrangement by which lymphatic trunks drain into subclavian vessels Under fluoroscopy the medium could be seen entering the peripheral portion of the node first With further filling the central portion became opaque and the medium then advanced to the next group of nodes via the efferent lymphatics

Inadequacies of Routine Bleeding and Clotting Times A routine laboratory test once well established is often slavishly adhered to with little thought about how it originated why it is done or what it means To justify it phrases for the record and for protection are often heard Tests done only for these reasons waste time and money and can be misleading giving the physician a false sense of security or causing concern over a potentially serious disease when none actually exists

Louis K Diamond and F Stanley Porter[3] (Harvard Med School) studied 36 children by peripheral blood examination determining bleeding time by the Ivy method clotting time by the Lee White method prothrombin time by the Quick method and by measuring prothrombin consumption and thromboplastin generation

Nine in group I had had routine determinations of clotting and bleeding times done in other laboratories before surgery and the results of one or both tests were reported abnormal The children were then referred to the authors for further examination None had had any family or past history suggesting a bleeding disorder and the physical examination was normal in all At examination none showed any coagulation defect or bleeding tendency

Eight children in group II had normal bleeding and clotting times but bled after tonsillectomy or tooth extraction None had a history of bleeding disorders and all were normal on physical examination All the special tests were negative

Nineteen in group III had had a family or past history of hemorrhagic disease and at operation proved to be bleeders Twelve had classic hemophilia and 7 Christmas disease yet tests showed their bleeding and clotting times to be

(3) New England J Med 59 10 5 10 N 20 1958

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(3) New England J Med 259 10 5 10 7 N 20 1958

high as 3 89% If the sample includes under 200 people the sampling error may be as high as 15%

Another source of error is often overlooked the technical error The blood tests are not always reliable In large groups errors of 2 1 88% have been reported As many as 10% of infants with blood group AB are wrongly classified as group B

Review of the data on blood group A and cancer of the stomach fails to show consistent results Even when a relationship is claimed it is of low order (4 8%) Taking into account the magnitude of variations because of natural differences in genetic make up of populations and inevitable sampling errors this lack of consistency is not surprising

Blood group O has been claimed to be of higher incidence among patients with peptic ulcer than among those in a control series The differences are more significant in peptic ulcer than in cancer of the stomach and tend to suggest that a relationship actually exists but the association is *not proved beyond doubt Analysis of sibships reported by Clarke in* 1956 gave no evidence to support the hypothesis that gr[illegible]up O persons were more likely to have a duodenal ulcer than were his A B or AB sibs Further refuting evidence has ac[illegible] crued from Great Britain in regions where incidence [illegible] blood group O is high incidence of peptic ulcer is n[illegible]t

Other attempts have been made to find possible a[illegible] tions between blood groups A B and O and other dise[illegible] The general background for such attempts is nearly [illegible] the same as that reviewed above There is partial or to[illegible] awareness of the magnitude of ethnic differences in the [illegible] group composition of populations and often uns[illegible] methodology

Weiner s comment is entirely justified While many p[illegible] pers suffer from the author s lack of knowledge of statistical methods more suffer from their misapplication Knowledge is no substitute for understanding and mathematics is a poor substitute for accurate observations reliable laboratory work and common sense

The wide and unqualified support given the view that blood groups A B and O are associated with certain diseases may prove warranted by future research but at present it is based largely on speculation

cells Perhaps this is due to removal of all plasma components leukocytes and platelets which is an incidental side effect of the glycerolization process inside the Cohn fractionator

Even after storage at very low temperatures for periods up to 19 months the red cells appeared therapeutically comparable to cells stored at 4 C up to 21 days in a standard ACD solution Red cell survival measured by Cr^{51} was independent of the duration of storage Loss of red cells by lysis during the process as a whole seemed to be entirely due to irreversible random damage during collection and handling rather than to storage at low temperature The closed system sterile method used for processing allowed use of standard refrigerator storage and blood bank methods after removal from the frozen state

Blood Groups and Disease—Hard Facts and Delusions Recent investigations have attempted to establish relationship between blood groups A B and O and certain diseases—carcinoma of the stomach duodenal and gastric ulcer diabetes mellitus pernicious anemia bronchopneumonia toxemia of pregnancy and others The conclusions usually have been based on comparison between a pathologic series from a hospital ranging from under 100 to over 1 000 cases and a control series usually blood donors from the same area

A critical analysis by Alexander Manuila[5] (Univ of Geneva) indicates that much of the evidence is of doubtful value and some is worthless When a difference is found between two samples comprising 500 1 000 persons from the same locality it may be due to (1) genuine differences in the ethnic and racial make up of the two samples (2) sampling errors (3) errors of technic and (4) other causes including possible relationship between blood groups and disease Anthropologists are constantly aware of differences existing even within small groups A difference of 5% or even 10% between two series cannot be attributed to any single cause unless there is reasonable evidence that the samples are statistically comparable

Many investigations fail to take into account the role played by errors from pure chance or bias When working with a population with an expected gene A frequency of 43% sampling 2 500 persons the sampling error may be as

(5) J A M A 167 2047 2053 Aug 3 1958

tissues with the production of oxygen carrying hemoglobin

The action of an anoxic stimulus on red cell production was studied in rabbits that were bled 20 ml/kg kept anemic for 20 hours then reinfused with the previously removed blood This 20 hour period was followed by a characteristic reticulocyte response which was modified by nitrogen mustard or colchicine given immediately after the 20 hours but was not influenced by anoxia or hyperoxia in the post anemic period When mitotic division was arrested by colchi

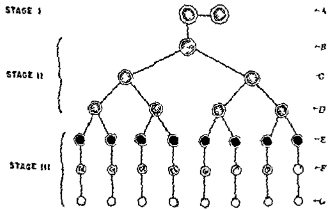


Fig 50 —O tl f d f pm t of n l t d d blood fl m w A t m
tl B pr m bl t C b soph l rm bla t D poly h m toph l rmobl ast
E rth h m t ph l m tl t F t locyt G m t ed l) (Court y E
E l A J Blood 14 386 398 Ap l 1959)

cine during the 20 hours of anemic anoxia onset of the reticulocyte response though delayed by 1 2 days was otherwise of characteristic magnitude

These observations indicate that the anoxic stimulus operates in the bone marrow by accelerating the differentiation of stem cells into pronormoblasts and that thereafter the maturation and multiplication of differentiated nucleated red cells proceed independently of the anoxic stimulus

Assay of Erythropoietin in Bone Marrow Suspensions Most methods for assay of erythropoietin use nonphysiologic preparations such as the hypophysectomized or starved animal although the results have been reliable when Fe^{59} incorporation into the erythrocyte is the measure of erythropoietic activity A recently developed method measures Fe^{59} incorporation by human bone marrow cultures The

REGULATION OF ERYTHROPOIESIS

► This section is concerned with the cellular dynamics and humoral control of erythropoiesis in the bone marrow by a plasma factor. Some aspects of the dynamics of other types of bone marrow cell proliferation as well are presented in the first 3 articles of the section on General Topics and Technics.—I d

Effect of Anemic Anoxia on Cellular Development of Nucleated Red Cells was studied by Allan J Erslev[6] (Harvard Med School) with the technical assistance of Elva Ruiz. A number of distinct functional stages can be recognized in the development of nondifferentiated stem cells to mature red blood cells. Several investigators have attempted to design a model of this process based on studies of bone marrow morphology, metabolism, mitotic activity and volumetric changes of the nuclei. From these studies emerges a rough outline of red cell development (Fig 50). Stage I represents the period in which an undifferentiated but multipotential stem cell is differentiated into an immature red cell, the pronormoblast. It appears that this process must involve a division where one of the resulting cells is differentiated into a pronormoblast whereas the other remains undifferentiated, thus preventing depletion of multipotential stem cells. Stage II represents the period in which maturation and hemoglobin synthesis take place concomitantly with mitotic division. The exact number of divisions is unknown but on the basis of bone marrow differential counts three divisions during stage II would appear to be a reasonable assumption. At the end of this stage the red cell nucleus has become pyknotic and probably incapable of further divisions. Stage III represents the period in which final maturation of the cytoplasm takes place with disappearance of mitochondria and ribose nucleic acid. The pyknotic nucleus is extruded and it appears unlikely that further multiplication takes place.

It is assumed that maturation and division of red cell precursors will go through these stages in an orderly manner if the necessary enzymes, hormones and metabolic building blocks are available. Under such conditions the rate of red cell production appears to be regulated solely by a feedback mechanism that balances the demand for oxygen in the

(6) Blood 14 386-398 Apr 1959

viously been found to be associated with a protein that had paper electrophoretic mobility of an alpha globulin and chemical characteristics of an acid glycoprotein Small molecular weight acidic glycoproteins are found in Cohn fraction VI and erythropoietic activity was found in this fraction of plasma from phenylhydrazine anemic rabbits

Acidified boiled plasma filtrate obtained from phenylhydrazine anemic adult white male rabbits was dialyzed lyophilized then fractionated on diethylaminoethyl cellulose ion exchange columns Subcutaneous injections were given daily for 4 days with respective fractions of the column to female Sprague Dawley rats On the 4th day the animals were given intravenous Fe^{59} as iron citrate The per cent of the injected dose appearing in the total red cell mass in 24 hours was estimated by standard scintillation counting

Erythropoietic activity was confined to a specific area in the ion exchange chromatograms Centrifuge data of the eluted material suggested that the active material had a molecular weight of about 10 000 Electrophoretic mobility corresponded to the mobilities of the alpha globulins migrating as a single component between that of alpha and alpha$_1$ It stains as a glycoprotein It has a low isoelectric point and small molecular size The protein content was estimated at 69 3% and sialic acid content at 15 6% Hexose content by anthrone reaction is 7 7% and glucosamine content 10%

This separation and isolation of erythropoietin is reproducible

Erythropoietic Principle in Blood of Rabbits Made Severely Anemic with Phenylhydrazine Peter H Lowy Geoffrey Keighley Henry Borsook and Ashton Graybiel[9] (California Inst of Technology) developed an assay for determining the erythropoietic factor in normal adult mice The advantages of the method are the short time required (4 days) the small amount of test material needed and the facility with which many tests may be run simultaneously

For measurement of Fe^{59} uptake a procedure was found that allows counting of whole dried blood with an end window Geiger Muller tube A procedure was also found for preparing highly active erythropoietic filtrates from the

(9) Blood 14 262 273 M b 1959

practical objections to current methods for assay of erythropoietin—expense in time animals and test material—can largely be obviated by measuring Fe^{59} incorporation into rat bone marrow cells in suspension

The method is described by Leslie R Schroeder Clifford W Gurney and Nancy Wackman[7] (Univ of Chicago)

METHOD —Bone marrow is taken from the femur and tibia of an adult rat made anemic by bleeding 4 6 days earlier The marrow is suspended in a mixture of two thirds Eagle s basal medium and one third serum normal or anemic to which a small amount of Fe^{59} ferric chloride has been added The nucleated cell count is adjusted to 10 15 000 cells/cu mm and 2 ml aliquots are distributed into silicone test tubes At the start and at intervals during incubation at 37 C the aliquots are analyzed The cells are separated by centrifugation washed with normal saline resuspended and radioactivity measured by a well type scintillation counter

The presence of one third anemic serum in the incubation mixture results in 2 hours in at least a twofold increase in radioactivity in the cells over that found in a suspension that contains one third normal serum If aseptic and incubated for 24 hours the incorporation in anemic serum is sevenfold that of normal serum The magnitude of the difference between control and test suspensions is a function of the amount of erythropoietin present the activity of the marrow and the time of incubation

► [The possible use of surviving marrow clearly offers advantages However another parameter not mentioned by the authors is also involved in the marrow function the cold iron content of the serum under test This may well be less for the anemic serum and therefore with a similar total iron uptake by the marrow a greater proportion will be the hot iron measured As seen in the previous article Ersley believes that erythropoietin primarily affects the early stages of marrow red cell division and that only later are subsequent stages involving iron incorporation accelerated In experiments shortly to be published he has shown that with bone marrow cell division in vitro inhibited by colchicine the radioiron uptake is less However even so anemic serum had no effect when the cold iron content of serum was controlled However Matoth *et al* (J Lab & Clin Med 51 420 1958) believe that they have demonstrated significant increases of early and intermediate normoblasts in vitro after 17 hours under the influence of hypoxic and anemic serums

The next 2 articles are careful studies of the nature of the erythropoietic material present in the boiled plasma of anemic animals —Ed]

Purification of Erythropoietin by Ion Exchange Chromatography has been accomplished by W A Rambach J A D Cooper and H L Alt[8] (Northwestern Univ) Erythropoietic activity of acidified boiled plasma filtrates prepared from phenylhydrazine anemic rabbits had pre

(7) Nat Lond 181 1537 1538 May 31 1958
(8) Proc S Exper Biol & Med 98 60 604 July 1958

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(9) Blood 14 6 273 M b 1959

boiled plasma of rabbits made severely anemic with phenylhydrazine

A true polycythemia can be produced in normal adult rats at ordinary altitudes by injection of the filtrate of boiled plasma of rabbits made severely anemic with phenylhydrazine All the criteria of polycythemia are observed increases in red blood cell count hematocrit and hemoglobin concentration reticulocytosis and evidence in the bone marrow of stimulation of erythropoiesis An extract of such anemic rabbit plasma is effective not only in the normal adult rat but also in mice Anemic dog plasma is active in the rat The active principle is clearly not species specific

The authors found that the ineffectiveness of whole anemic plasma and the effectiveness of the filtrate after the plasma is boiled is associated with the respective presence and absence of antibody provoking antigens

A fractionation procedure was used whereby a fraction was obtained which on the basis of amount of protein is much more potent than unfractionated plasma filtrate by tests based on reticulocytosis in mice Fe^{59} uptake in starved rats and polycythemia in normal rats When this material was subjected to zone electrophoresis two thirds of its protein and all the activity was confined to one band Notably the material which gave the positive responses to the three tests has thus far remained together in one fraction

The erythropoietic activity of plasma filtrate and other plasma fractions was always associated with protein whether measured by the biuret or Folin phenol reagents Activity was completely lost after digestion overnight at 36 degrees with 0 1% trypsin or chymotrypsin The activity remained after standing at pH 10 9 at room temperature for 21 hours It was lost completely after 16 hours at 36 degrees at pH 1 6 Only a fraction of the erythropoietic activity in anemic plasma is recovered in plasma filtrate Much of this loss is due to entrapment in the heat coagulated proteins Thus far erythropoietic activity has been inseparable from protein Electrophoresis showed somewhat different mobilities from those of the active material of Rambach *et al* but chemical tests agreed in indicating the presence of a mucoprotein [See preceding article —Ed] Several hormones vitamins and other growth promoting materials were tested for erythropoietic activity with negative results

HEMOLYTIC ANEMIAS

Immunologic Differences between Isoantibodies and Autoantibodies In acquired hemolytic anemia a gamma globulin coating the erythrocytes is the warm acting isoantibody In many instances its presence is detected only when the cells are suspended in special mediums anti human globulin (Coombs) serum is used or when the patient s plasma is tested with enzyme treated red cells Such findings are also typical of cells coated with incomplete isoantibody [e g anti Rh antibody—Ed] Obvious sensitization however is not present in acquired hemolytic anemia of idiopathic and secondary types so the concept of autoimmunization has been developed This is based on the premise that the coating material represents an autoantibody which is the sequela of active immunization against an antigen in the patient s own cells Such antigens have not been shown and the theory violates the law of horror autotoxicus

Bernard Pirofsky[1] (Univ of Oregon) obtained warm acting erythrocyte coating material (ECM) washed free from serum proteins from 4 patients who had acquired hemolytic anemia secondary to chronic lymphocytic leukemia with positive direct anti human globulin (Coombs) test Using an indirect Coombs procedure and a panel of erythrocytes that contained C D E V c e f K k Fy Le Le^b Jk Jk^b M N S s P and Lu the four solutions coated erythrocytes in a pattern unrelated to the presence of the antigens listed The coating materials seemed to act as panhemagglutinins

Eluates of red cells ensitized with anti Rh (D) titer 1 16 to 1 32 and of anti rh (C) serum with titer of 1 128 to 1 256 yielded virtually identical reaction with anti human globulin serums When the eluates were mixed with various anti human globulin serums refrigerated 24 hours then tested for available isoantibody and available anti human globulin antibody the action of the incomplete isoantibody was inhibited Inhibition was complete in the weak eluate containing anti Rh (D) and less pronounced when the potent eluate with anti rh (C) was u ed

The ECM from the 4 patients yielded eluate with a po

(1) Am J Cl P th 1 0 127 F b y 19 8

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don) studied the survival of small amounts of incompatible red cells after labeling them with Cr^{51} or P^{3} in healthy persons whose serum contained some unusual antibody in patients who had already received several transfusions and had antibodies and in volunteers whose own red cells were treated with incompatible antibody before being labeled and reinjected

About 1 ml donor red cells was labeled with Cr^{51} and 1 3 ml of the subject s own red cells was labeled with P The mixed cells were suspended in about 25 ml ice cold saline and 20 ml was injected in 30-60 seconds After injection of the incompatible cells 6 10 blood samples were taken the first 2½ 3 minutes after injection and the last about 1 hour later The rate of disappearance of Cr^{51} corrected for zero time by P^{3} measurement was taken as the rate of donor cell removal

Anti A and anti B antibodies which are strongly agglutinating and lytic or potentially lytic in vitro were the only *antibodies encountered which brought about the intravascular* destruction of a large fraction of the injected red cells Almost all cells were removed within 3 minutes and a large proportion of the radioactivity appeared in the plasma

Other agglutinating antibodies that either agglutinated strongly in vitro or fixed complement sometimes brought about the removal of red cells with a half time of 2 6 minutes although often only 15 50% of the cells were destroyed Antibodies which did not agglutinate saline suspensions of red cells in vitro but sensitized them to an anti non gamma globulin serum (i e antibodies which bound complement) also brought about the removal of red cells with a half time of 2 6 minutes

Agglutinating antibodies which did not react strongly in vitro and did not fix complement brought about the removal of red cells with a half time of about 20 minutes or more Antibodies which did not agglutinate saline suspensions of red cells in vitro but sensitized them to an anti gamma globulin serum and not to an anti non gamma globulin serum also brought about the removal of red cells with a half time of about 20 minutes or more

It has been shown that removal of red cells with a half time of 20 minutes represents predominantly splenic destruction and that removal with a half time of 2-6 minutes

tency that ranged from 1 16 to 1 64 all giving similar reactions with anti human globulin serums When mixed with various anti human globulin serums refrigerated for 24 hours then tested for available ECM and anti human globulin antibody the ECM potency did not decrease When the ECM was serially diluted with isotonic saline then mixed with anti human globulin serums and tested for available ECM again no inhibition of activity as an apparently incomplete autoantibody was demonstrated

The ECM was heated to 56 C for 30 minutes without loss of potency but when heated to 70 C for 30 minutes activity was completely lost This indicated that the ECM might be a protein which was confirmed by electrophoresis and fractionation The active material migrated as a slowly moving gamma globulin

Leukemic ECM reacts with anti human globulin serum in the presence of erythrocytes but not when erythrocytes are excluded from the system It seems that ECM must coat erythrocytes before the reaction with anti human globulin serum occurs Coating of erythrocytes seems to involve linkages not included in the reaction with anti human globulin serum Apparently the coating allows reaction with anti human globulin serums Still undetermined is whether the relation is characteristic for all autoantibodies or specific for ECM found in patients with chronic lymphocytic leukemia complicated by acquired hemolytic anemia

► [In addition to the possibility that the ECM coating the red cells in acquired hemolytic anemia is an *incomplete antibody* or *autoantibody* is the possibility that it is no such thing but *merely a consequence* of perverted or neoplastic production of proteins that fortuitously attach to the red cell as for example in the case of red cell agglutinins of plant origin (lectins) Indeed that the Coombs test is an immunologic procedure has no bearing whatever on the *origin* of the coating on the red cell Thus the authors cite the work of Muirhead and of Sutherland and Eisenstaut who observed positive Coombs tests in animals with hemolytic anemias due to phenylhydrazine and lead intoxication respectively These observations probably depend on the fact that reticulocytes are coated and Coombs positive as recently pointed out by Jandl (*J Clin Invest 37* 905 1958) Jandl and Simmons (Brit J Haemat 3 19 1957) have also shown that no immunologic mechanism is required for the production of red cells with a positive Coombs test if they are exposed in vitro to certain polyvalent cations in the presence of serum On this basis the lack of a demonstrable autoantigen so embarrassing to the immunologist is obviated —Ed.]

Relation between Characteristics of Blood Group Antibodies in Vitro and Associated Patterns of Red Cell Destruction in Vivo Marie Cutbush and P L Mollison (Lon

(2) Brit J Haemat 4 115 137 Apr 1958

of 9 days and this was even shorter in an infant with an intact spleen The inclusion bodies had disappeared from the recipient s circulation by the end of 24 hours

Several findings point to a probable erythrocytic metabolic defect (1) abnormal bile pigment production associated with intracorpuscular erythrocytic defect and (2) chemical changes of increased nucleic acid in the inclusion bodies and probable glutathione abnormalities However the exact metabolic defect is unknown The urinary pigment *probably belongs to the bilifuscin and mesobilifuscin* groups The *syndrome is believed to be caused by an inborn* error in erythrocytic metabolism and because of the character of the inclusion bodies to be different from other instances of congenital Heinz body anemia

Hereditary Anemia with Hemochromatosis Studies of Unusual Hemopathic Syndrome Resembling Thalassemia are reported by Armand P Gelpi and Norman Ende[4] (V A Hosp Fresno Calif)

Two brothers descended from Swiss English German stock have a refractory anemia similar in many respects to Mediterranean anemia In one 33 years old the anemia became so severe in association with fever and arthralgia over several weeks that he spent 18 months in the hospital The other has never been hospitalized and aside from having a mild hypochromic anemia appears to be in good health Basic hematologic data from members of the immediate family indicate that the mother and sister may be carriers of the defect Both brothers have malformed red cells which show increased osmotic resistance No autoimmune hemolytic system is present Abnormal hemoglobins have not been found Alkali resistant or fetal hemoglobin is not present and there is no micro or leptocytosis The red cells have a shortened life span accounting in part for the severe anemia Splenectomy in the more severely affected brother produced temporary benefit and prednisone also caused temporary slight amelioration of the anemia Further complications in this brother are hemochromatosis recurrent thrombophlebitis and a localized peritonitis presumably due to perforation of an acutely developing duodenal ulcer Blood smears show that the red cells are strikingly abnormal *in structure* and contain many normoblasts (Fig 51)

(4) Am J Med 5 303 314 Aug t 1 58

represents predominantly hepatic destruction The present observations thus suggest that cells which carry bound complement are far more readily removed by the liver than cells which do not Nevertheless the differences between splenic removal and hepatic removal may be essentially quantitative cells which are only slightly altered being far more readily removed by the spleen than by the liver

► [These results are consistent with the observations of Jandl *et al* (J Clin Invest 36 1428 1957) in which body surface radiation over the liver and spleen was in addition carried out—Ed]

Congenital Hemolytic Anemia with Abnormal Pigment Metabolism and Red Cell Inclusion Bodies New Clinical Syndrome is described by Robert D Lange and Joseph H Akeroyd[3] (Walter Reed Army Inst of Res) Abnormal inclusion bodies are known to follow ingestion of toxic substances The girl in this study aged 14 had known hemolytic anemia since age 30 months but there was no history of ingestion of toxic substances The urine was dark brown or black An enlarged spleen had been removed at 4 years and 4 months

Laboratory examinations showed red blood cells 3 000 000/cu mm hemoglobin 8 5 Gm /100 cc mean corpuscular volume 103 cu μ mean corpuscular hemoglobin concentration 27% reticulocytes 19 5% total white blood cells 8 150/cu mm and platelets 585 000/cu mm The red cells showed extreme anisocytosis and poikilocytosis polychromatophilia basophilic stippling spherocytosis target cells Howell Jolly bodies and bizarre inclusion bodies which remain unclassified They do not resemble Pappenheimer bodies in that they are not rodlike They are not siderin Many siderin granules were present in the erythrocytes and the abnormal inclusion bodies showed a rim of iron staining material The inclusion bodies resembled Heinz bodies in some morphologic and physical characteristics in that they were globular refractile and irregular in shape stained with crystal violet and insoluble in water However they were visible when stained with Romanowsky dyes whereas Heinz bodies are visible only by vital dyes or darkfield microscopy

Osmotic fragility was moderately decreased mechanical fragility was increased three or fourfold With Cr^{51} labeling normal cells transfused into the patient survived almost normally The patient s cells in the patient had a half life

(3) Blood 13 950 958 October 1958

of 9 days and this was even shorter in an infant with an intact spleen The inclusion bodies had disappeared from the recipient s circulation by the end of 24 hours

Several findings point to a probable erythrocytic metabolic defect (1) abnormal bile pigment production associated with intracorpuscular erythrocytic defect and (2) chemical changes of increased nucleic acid in the inclusion bodies and probable glutathione abnormalities However the exact metabolic defect is unknown The urinary pigment probably belongs to the bilifuscin and mesobilifuscin groups The syndrome is believed to be caused by an inborn error in erythrocytic metabolism and because of the character of the inclusion bodies to be different from other instances of congenital Heinz body anemia

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(4) Am J M d 5 303 314 A g t 1958

The anemia resembles the sex linked or sex influenced anemia originally described by Cooley Because of the striking similarity to moderate or severe thalassemia in terms of red blood cell morphology and evidence of a poorly compensated hemolytic process the term pseudothalassemia is suggested for this type of hemopathic disorder It is postulated that there is a defect in the synthesis of hemoglobin or in the effective release of erythrocytes from the marrow similar to that which is considered present in and explanatory



Fig 51—Str king t tu al lte t s of d bl od ll a d n m bl t du g p od f m k d yth d hyp pl mo ly ffect d b th W ghts t (C rt y of C lp I a d End N Am J M d 25 305 314 Aug t 1958)

of the essential erythropoietic deficiency in thalassemia Unlike the patients recently reported by Harris and co workers there was no response to 3 weeks of parenteral therapy with pyridoxine

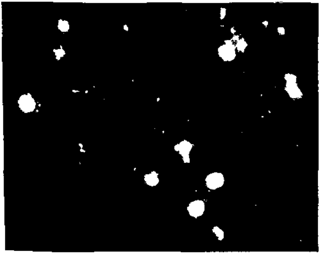
Hematologic Aspects in Case of Erythropoietic Porphyria are described by S Varadi[5] (Sheffield England) This disease previously labeled congenital porphyria is really a disorder of the erythropoietic system It appears to be genetically determined and is probably recessive in inheritance

Girl at birth excreted meconium which stained the diapers pink The urine was pink at first but by 2 months was dark red She seemed pale but otherwise was healthy and fed well The spleen and liver were felt 4 and 2 cm respectively below the costal margin at 5½ months She appeared pale and had persistent marked thrombocytopenia and anemia A 95 Gm spleen was removed which was dark brownish red and showed an intense red fluorescence under ultra

(5) Brit J Haemat 4 270 80 July 1958

violet light The urine remained pink but never regained its pre splenectomy burgundy red or dark brown color

The first tooth cut a month after splenectomy showed brown dis coloration Hypertrichosis gradually developed mainly on the fore head along the hairline Three months later typical blisters of hydroa vacciniforme appeared on the face and hands Shielding from the sun and administration of 50 mg chloroquine daily resulted in improve ment During the summer the fingernails became dystrophic and by



F g 5 —B w film h w g fl sc t m bl t n l lt l t light Rodl k t t be n yt pl m f on m bl t d g l th N t g p f f n m bl t f tly fl ent d ll d d f m ×1000 (C rt f V d S B t J H m t 4 0 2 0 J ly 1958)

the end of July were nearly all shed They were replaced by new ones which appeared normal and blisters ceased forming in October

At age 2 the patient had many reddish brown superficial scars on the fingers hand and wrists Hypertricho is was marked hair was 2 cm long on the outer aspects of the forearms and arms and she had strikingly long eyelashes All 20 teeth were deep purple near the gums which were similarly colored the color gradually fading to ward the tooth margins

Before splenectomy the red cells were normochromic with poly chromasia anisocyto is poikilocytosi and slight microcytosis Many cells were stippled with a peculiar dark almost black hue The retic ulocyte count was raised and about 5% of the red cells and some nor moblasts showed red fluorescence in ultraviolet light The bone marrow showed normoblastic hyperplasia and many normoblasts showed peculiar degenerative changes Many normoblasts gave a rich red fluorescence strongest in the nuclei under ultraviolet light (Fig 52)

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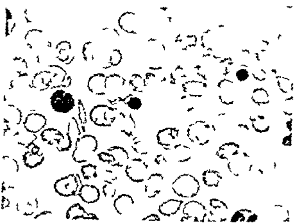


Fig 51 —St k ng t u ru al lt t s f d blood ell a d norm blasts d f p od f m k d yth d hyp pl a n m ely affect d b th Wrights stain (C rt y of Gelp A P al End N Am J M d 25 303 314 August 1958)

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pared fresh by dissolving 5 000 units of powdered bovine thrombin in 10 ml serum Properdin was removed by incubating for 2 hours at 17 C with activated zymosan 2 mg/ml erum After incubation no properdin could be demonstrated

The serum thrombin mixture increased hemolysis when added to the PNH cell suspensions Previous treatment with zymosan diminished only slightly its ability to alter the intensity of the reaction Similar results were obtained when the thrombin test was performed using thrombin preparations heated to destroy properdin Even when zymosan treated solutions were passed through cation exchange resins to remove all Mg^{++} the activity remained

If incubation with zymosan or heating at 56 C removes or inactivates the properdin in serum these studies indicate that the properdin which contaminates thrombin preparations has little to do with the results of the thrombin test The increased hemolysis produced by adding thrombin to the PNH hemolytic system in vitro may be due to some action of thrombin itself to a degradation product of thrombin or to a contamination other than properdin

The coagulation mechanism is probably involved because thromboplastin has the same effect as thrombin and the addition of platelets during the clotting of platelet poor plasma greatly increases the hemolytic activity of the serum formed Both platelets and thromboplastin are devoid of properdin activity

► [These observations if confirmed appear to settle a controvers al issue in which other have claimed that the observed effects of thrombin were due to contamination by properd n —Ed]

Mechanism of Action of Preparations of Thrombin on Hemolysis of Red Cells from Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) has been ascribed by Crosby to decrease of the activity of an inhibitor present in normal serum This he believes is the basis of the augmented hemolysis that follows the addition of thrombin preparations to suspensions of PNH red cells in acidified normal human serum Hemolysis of PNH red cells in vitro requires components of normal human erum properdin certain fractions of complement and magnesium ions Carl F Hinz Jr[7] (Western Reserve Univ) with the technical assistance of M Jane Dallas states that bovine and human thrombin

(7) J Lab & Cl Med 8 283 A g t, 1958

Splenectomy was followed by a decrease in hemolysis and diminished erythropoietic activity of the bone marrow The hemoglobin eventually reached 12 2 Gm /100 ml and the platelet count rose above normal The striking feature of the immediate postoperative period was the increased number of red cells containing needle like structures in the peripheral blood A month later these decreased The needles stained blue or purple with Leishman or May Grunwald Giemsa stain They were thin single or multiple and often associated with the peculiar granular stippling These needle like structures probably porphyrins were found in some abnormal normoblasts and nonnucleated red cells They have not been reported previously

The fundamental defect in erythropoietic porphyria is thought to be a genetically determined fault in the enzyme systems controlling heme synthesis which results in the production of abnormal porphyrin type I isomers along with normal type III isomers Splenectomy removes a filter capable of selective elimination of the porphyrin laden (needle like crystals) red cells and of too many platelets A vicious circle is cut and the reduced erythropoietic activity of the bone marrow results in decreased abnormal porphyrin production

Paroxysmal Nocturnal Hemoglobinuria Role of Properdin in Diagnostic Thrombin Test Red blood cells in patients with paroxysmal nocturnal hemoglobinuria (PNH) are susceptible to hemolysis by factors which occur naturally in plasma Hemolysis occurs readily in vitro and is intensified when the incubating mixture has been made slightly acid In patients with PNH hemolysis is sometimes associated with increased blood coagulation In vitro hemolysis can also be increased by adding to the Ham test small amounts of thrombin or thromboplastin

Recent studies have shown that the PNH hemolytic system depends on the bactericidal globulin properdin Properdin plus Mg^{++} and other plasma factors can hemolyze PNH cells in acidified serum Commercially available preparations of thrombin used for the thrombin test are contaminated with properdin suggesting that the effect of thrombin on the PNH hemolytic system is due to the contaminating properdin

William H Crosby and Naomi R Benjamin[6] (Walter Reed Army Inst of Res) studied PNH red cells from 3 patients with a classic history and signs of the disease Serum was acidified just before the test Thrombin solution was pre

(6) Blood 13 684 687 July 1958

pared freshly by dissolving 5 000 units of powdered bovine thrombin in 10 ml serum Properdin was removed by incubating for 2 hours at 17 C with activated zymosan 2 mg/ml serum After incubation no properdin could be demonstrated

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(7) J [illegible] M [illegible] 52 82 298 A[illegible] 1958

preparations devoid of properdin activity and rendered almost free from clotting activity were still capable of augmenting hemolysis in vitro of red cells from 2 PNH patients

The test system was a 1 10 suspension of washed PNH red cells in slightly acidified normal human serum buffered at pH 6 8 and incubated at 37 C for 30 minutes The total volume of thrombin preparations added was always less than half that of the normal serum to avoid diluting the serum s hemolytic activity Hemolysis was determined by colorimetric measurement of the hemoglobin in the supernate agglutination of red cells by macroscopic inspection of the sediment after centrifugation for 2 minutes at 1 800 g

Four preparations of bovine thrombin agglutinated human red cells and one preparation of human thrombin agglutinated group A but not group O red cells Augmentation of hemolysis of PNH red cells paralleled the agglutinating activity of these thrombin preparations which did not hemolyze normal red cells in the test system Heating the thrombin preparations to 56 C for 30 minutes greatly reduced their thrombic but not their agglutinating or hemolytic activities for PNH red cells The human thrombin preparation augmented hemolysis of group A PNH red cells but not that of group O PNH red cells Its agglutinating and hemolysis augmenting properties were reduced by adsorption with group A red cells or by addition of group A substance without effect on its thrombic activity

It is well known that PNH red cells are susceptible to hemolysis by agglutinating antibodies in conventional systems Consequently the authors conclude that the basis of the hemolysis augmenting effect of thrombin preparations devoid of properdin activity is their content of antibody like (agglutinating) substances and not their thrombic activity for blood coagulation

► [This is in accord with the conclusions of the authors of the preceding article in excluding contamination by properdin It provides a clarifying explanation of the phenomenon which according to them somehow improves the effectiveness of the hemolytic factors already present —Ed]

Serologic Studies on Favism were done by S Zvi Kantor and Carl L Arbesman[8] (Univ of Buffalo) Favism is a disease characterized by acute hemolytic anemia with hematuria and jaundice It is produced by ingestion of the broad

(8) J All gy 30 114 1 M Ap 1959

bean (Vicia fava) or by inhalation of its pollen when the plant is in bloom

The authors found a substance in a 1 480 dilution of the serum of a patient with acute untreated favism and in 1 128 000 dilutions of the serum of rabbits immunized with fava bean extract that had the ability to cause agglutination of human group O Rh negative red blood cell previously treated with tannic acid and exposed to fava bean extract The reaction was specific and hemagglutination of tanned red blood cells treated with extracts from other types of beans was minimal or did not occur The specificity was also confirmed by the specific inhibition reaction Patients with favism who had been treated by blood transfusions and re covered failed to show this type of antibody

The pathogenesis of favism is not definitely known A toxic mechanism is suggested by the presence of plant agglu tinins in the bean families including fava bean In the pres ent studies fava bean extract in dilutions greater than 1 5 did not produce lysis of the tannic acid treated red blood cells in the test tube However navy bean and kidney bean extracts which do not produce hemolytic disease in vivo did cause lysis of these cells in vitro in dilutions of 1 20 and 1 30 respectively

Favism has been compared to the drug induced hemolytic anemias (due to sulfonamides primaquine or naphthalene) and comparable evidence of metabolic changes such as glu tathione deficiency in the red blood cells of patients has been shown Although a hereditary and individual hypersensitiv ity factor in the disease is not excluded a true immunologic hypothesis is ignored

Other authors conceived the allergic theory Glaser defined favism as a disease due to allergy to the fava bean Preti was the first to use the term anaphylactic syndrome as related to favism According to Wintrobe incomplete red blood cell antibodies are present in the patient s serum In his review of the immunology of hemolytic anemias Mil rom stated that autoimmunization occurs in hypersensitive persons Besides in vitro and animal experiments it is estab lished that direct skin tests as well as Prausnitz Kustner tests are positive in patients after recovery but are absent in the acute stage of the disease (desensitization phenome non?) That favism does not occur on the first ingestion of

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sus In any such evaluation the fact that systemic lupus erythematosus is not necessarily a rapidly and progre sively fatal disease is an important consideration Its course may be one of spontaneous remissions and exacerbations with periods free from detectable disease A similar cyclic course may also characterize acquired autoimmune hemolytic anemia

Patients with acquired autoimmune hemolytic anemia complicating systemic lupus erythematosus should be managed the same as patients with idiopathic autoimmune hemolytic anemia In patients with severe anemia transfusions may be lifesaving despite the fact that transfusion reactions readily develop in these patients Even if the greatest care is used in selecting blood for transfusion they may still have a pla ma reaction Under any circumstances packed erythrocytes are preferable to whole blood

Steroid therapy is still the therapy of choice Cortisone 400 mg or 150 units of ACTH daily in divided doses can be used initially Patients who do not show adequate response to this therapy should undergo splenectomy This was performed in 3 of the authors patients After splenectomy 2 patients required only small to moderate daily doses of steroids whereas 1 patient had been taking no medication and required no blood transfusions for 12 months Hematologic compensation appeared to be complete in all 3 instances and the manifestations of systemic lupus erythematosus were minimal or absent

Splenectomy in Hemolytic Anemia Results Predicted by Body Scanning after Injection of Cr^{51} Tagged Red Cells Certain types of hemolytic anemia particularly hereditary spherocytosis improve strikingly with splenectomy but results in other types have generally been unpredictable Paul R McCurdy and Charle E Rath[1] (Georgetown Univ) with the technical assistance of Kenneth McCoy evaluated 50 patients with hemolytic anemia including 10 in whom splenectomy was done

METHOD —Venous blood was withdrawn mixed with Cr 1 incubated then reinjected intravenously The anterolateral projection of the spleen was immediately monitored with unidirectional scintillation counter Venous blood was taken at 15 and 30 minutes to determine blood volume by conventional dilution technics and red cell survival After equilibrium over the spleen the anterior projections of

(1) New E gla d J Med 59 459 463 S pt 4 19 8

the bean or on first exposure to its pollen is well known The patient has to be first sensitized to become ill Eosinophilia is always present during an attack It has been observed that when prolonged rain produces a low pollen season the frequency of favism is diminished

Although a hemagglutinating antibody was found in the serum of a patient with untreated favism this does not preclude allergy or immunology as the pathogenic factor in favism The other factors mentioned must be considered as etiologic agents This is the first report in which antibodies were demonstrated by means of hemagglutination to the fava bean in vitro in a patient with untreated favism

Role of Splenectomy in Management of Acquired Autoimmune Hemolytic Anemia Complicating Systemic Lupus Erythematosus was studied by Harry E Sarles and William C Levin[9] (Univ of Texas Galveston) Autoimmunization plays a prominent role in the pathogenesis of acquired hemolytic anemia complicating systemic lupus erythematosus although the mechanism of formation of antierythrocyte antibodies remains obscure The following possible mechanisms for autoantibody production are proposed (1) hyperplasia of the reticuloendothelial system and lymphatic tissues in systemic lupus erythematosus may lead to overproduction and abnormal character of antibodies (2) autoantibody production may be just another manifestation of disordered protein metabolism found in systemic lupus erythematosus (3) cross reactivity due to antigens found in nature similar to the blood group antigens may produce antibodies that will react to the blood group antigens and (4) repeated stimulation with an antigen may in time lead to formation of antibodies which lose their specificity for the original antigen and will react to one of the blood group antigens

Although most of the accumulated evidence regarding the pathogenesis of acquired hemolytic anemia complicating systemic lupus erythematosus incriminates autoantibodies as responsible for the hemolysis other factors are involved This is supported by studies which show that erythrocytes coated with autoantibodies transfused into normal recipients may survive normally

There is a divergence of opinion regarding the effect of splenectomy on the course of systemic lupus erythemato

(9) Am J Med 6 547 554 Ap 1 1959

splenectomy The indexes employed are probably no more useful prognosti cally than Jandl s simpler formula R R₀. Here the initial relative per centage of radioactivity of spleen compared to precordium (R) is sub tracted from that at the red cell half survival time (R) —Ed]

PERNICIOUS AND OTHER NUTRITIONAL MACROCYTIC ANEMIAS

Advantages of Cobalt [5] Tagged Vitamin B_1 in Study of Vitamin B_1 Absorption Co^{60} has been used in most re ported studies but it has a physical half life of over 5 years and the possible danger of prolonged irradiation has caused some concern Co [8] has a half life of only 72 days

J L. Hutchison S R Townsend and *Douglas G Cam eron*[2] (McGill Univ) studied 44 patients including 15 con trols 13 who had pernicious anemia in remission 6 in relapse 3 with intestinal malabsorption 3 with subtotal gas trectomy and 4 with gastric achlorhydria but without hema tologic disease A modified Schilling technic was used 0 5 µg vitamin B_1 tagged with 0 4 1 2 µc Co^{58} was given to fasting patients One hour later 1 000 µg crystalline vita min B_1 was given intramuscularly The 24 hour urine ra dioactivity was compared with the radioactivity of the oral dose

Normal values ranged from 17 5% to 46% of oral dose In pernicious anemia the range was 0 54 5 8% There was no overlap between these two groups Results in the other three groups were less clear cut The values in 1 of the 3 patients with intestinal malabsorption fell in the pernicious anemia range (2%) whereas the values in the other 2 (6% 13%) were somewhat higher but still below normal One patient with subtotal gastrectomy was in the pernicious anemia range (3%) 1 (25%) was normal and 1 (13%) was in be tween The 4 patients with gastric achlorhydria had values close to the normal range (14% 16% 18% 20%)

An oral dose of 1 µc vitamin B_1 Co [8] permitted a clear differentiation between normal persons and patients with pernicious anemia without resorting to urine concentration

[Few untreated patients with vitamin B deficiency require more than usual clinical and laboratory appraisal of blood gastric and intestinal function plus a 10 day therapeutic trial to define the probable nature and

(2) C d M A J 8 685 68 M 1 1958

the liver heart and spleen were counted Ratios were constructed between the spleen and precordium and liver and precordium This calculation was made

$$\frac{\frac{\Delta S/P}{S/P} \times 10}{d_m} = \text{splenic localization index}$$

where $\Delta S/P$ is the maximum change in the ratio S/P i the initial ratio d_{max} is the day on which the maximum ratio occurs

In general the patients in whom benefit from splenectomy might be anticipated had maximum spleen and precordium ratios of 1 5 or more and splenic localization index of 1 or more The liver and precordium ratios were generally below 1 except in 1 patient with acquired hemolytic anemia who did not improve after surgery in 2 with sickle cell anemia in 2 with polycythemia and in 1 each with hypersplenism liver disease chronic lymphocytic leukemia chronic renal disease idiopathic anemia and systemic lupus erythematosus

Initial equilibration information the time taken to reach a plateau in counting over the spleen after injection of the Cr^{51} cell was not helpful in the decision for or against splenectomy If the time for reaching the plateau is markedly prolonged surgery will probably be beneficial

The combination of a splenic localization index over 1 and spleen and precordium maximum over 1 5 and definite need for further hematologic therapy in a patient with hemolytic process are sufficient to recommend splenectomy Of 10 patients who had splenectomy 9 fulfilled these criteria and did well

In three different investigations using similar methods for measuring radioactivity over the spleen and liver in 27 patients (including the authors 10 patients) the test results were positive for spleen localization in 25 Results of splenectomy were good in 22 in 2 not stated but were expected to be good and in 1 fair In 2 patients in whom the test was negative splenectomy gave poor results

The test based on the maximum spleen and precordium ratio splenic localization index and clinical picture appears reliable in selecting patients who have hemolytic anemia for splenectomy

► [This is a useful survey of the results to date of the splenic uptake of Cr^{51} labeled autogenous red cells as a means of predicting the effect of

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(2) Ca d M A J 78 685 687 M y 1 1958

mechanism of the deficiency Availability of B Co^{60} to clinicians has been convenient and especially useful in treated patients who did not originally receive adequate study but it has been much more important as a research tool Since despite permissible standards it is impossible to know that any isotope may not eventually cause damage there should always be adequate clinical indications for the diagnostic use of radioactive cyanocobalamin just as for example in the case of the usual gastrointestinal x ray series Now that B Co^{56} with a half life of 72 days instead of the 5 years for B Co^{60} is available it is reasonable that it be substituted for B Co^{60} wherever possible The present authors demonstrate that equally satisfactory measurements can be made with it They thus move the matter for consideration into the area of availability and cost of the isotope However the evaluation of the need for such a diagnostic measurement in a particular patient remains for his physician to decide with the knowledge that by the use of B Co^{58} any theoretical risk of the test may be decreased —Ed]

Quantitative Assay of Intrinsic Factor Activity by Urinary Excretion of Radioactive Vitamin B_{12} A standardized technic is outlined by Leon Ellenbogen and William L Williams[3] (Pearl River N Y) that has the particular advantage of allowing consecutive assays of up to 18 intrinsic factor preparations in the patient with pernicious anemia

METHOD —Each test dose of vitamin B_{12} Co^{56} or $B_{12}Co^{60}$ consists of 2 μg vitamin B_{12} and 0 25 μc radioactivity These are stored at −20 C in small vials until used Each dose is given in the fasting state or between meals Immediately after the oral dose of radioactive vitamin B_{12} 1 mg nonradioactive B_{12} is injected intramuscularly A second flushing dose of 1 mg nonradioactive B_{12} is given 24 hours after each dose of radioactive B_{12} This procedure is repeated with a reference intrinsic factor sample and with each intrinsic factor sample assayed Immediately before use intrinsic factor is mixed with the radioactive B_{12} solution in cold tap water The radioactivity of each 24 hour urine specimen was determined in a well type scintillation crystal

Successive urinary excretion tests were possible by using vitamin B_{12} Co^{56} (half life 72 days) The higher energy gamma rays allowed more sensitive counting and the short life allowed use of over 3 μc isotope thus permitting more consecutive urinary excretion studies in the same patient The repeated flushing doses had little effect on response in the urinary excretion test Excretion of vitamin B_{12} increased with increasing amounts of intrinsic factor in each of four different preparations indicating that large amounts of intrinsic factor did not inhibit absorption There was no relation between the urinary excretion values with radioactive B_{12} alone compared with radioactive B_{12} plus

(3) Blood 13 58 588 J 1958

standard intrinsic factor in 127 patients with pernicious anemia

In evaluating preparations total rather than net excretion values are preferred Patients with pernicious anemia who are given intrinsic factor absorb over 0 5 µg radioactive B_1 Therefore an oral dose of 2 µg vitamin B_1 which allows absorption of over 0 5 µg is preferred to extend the range of intrinsic factor test doses that can be assayed

Influence of Calcium Ions on Vitamin B_1 Absorption in Steatorrhea and Pernicious Anemia Ralph Grasbeck Ilmari Kantero and Max Siurala[4] (Univ of Helsinki) conducted

EFFECT OF ORAL CALCIUM ADMINISTRATION OF SCHILLING TEST VALUES OF PATIENTS WITH STEATORRHEA AND PERNICIOUS ANEMIA

Ca	Cl cal d t	S hill g t f (u ry d ct y a f 1d)	
		U al t t	W h al um
1	Id op thı s t rth f mal ag d 6 (A H)	0 3	20 1
2	Id p th t hœ f mal 51 (H)	3	7 5
3	Idı p h hœ rrhos m l 56 (H)	0	0 3
4	L n t hœ m l 54 (A)	0 1	4 4
5	Cœl dı mal 1 y	1 5	2 4
6	Cœlı d as mal 1 y	5 5	8 4
7 12	P rnı æmı 2 m l d 4 f m l g d 59– 0	0–1 7	0–1 7

A = m g l bl t m p d g t t m B B = hypoc l m gn

two Schilling tests about a week apart in 12 patients 4 with steatorrhea 2 with celiac disease and 6 with pernicious anemia The oral dose was 1 µg vitamin B_1 Co^{60} the 1 mg flushing dose was injected 90 minutes after the oral dose and the urine was collected for 24 hours In one test calcium lactate was used also half the dose being given 30 minutes before the radiovitamin and the rest simultaneously The dose of calcium lactate was 7 Gm for adults and 2 Gm for infants Results (table) indicated no definite effect of calcium on vitamin B_1 absorption in pernicious anemia but definite increase in steatorrhea

Herbert has shown that intrinsic factor preparations in the absence of calcium ions do not stimulate the uptake of vita

(4) L t 1 34 T 31 1959

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(3) Blood 13 592 588 J 1958

the rat intestine was susceptible to the greatest stimulation of B_{12} uptake in the presence of intrinsic factor

Intrinsic factor was not adsorbed to the intestinal epithelium since 1 rinse completely removed its activity from the tissue Only when B_{12} and intrinsic factor were present simultaneously was there uptake of B_{12} by the intestinal wall

► [These results differ from those of Herbert referred to in the preceding editorial comment principally in that the hog intrinsic factor used by Herbert does not enhance the uptake of B Co[60] by the gastrectomized rat whereas rat intrinsic factor does Moreover in these experiments it was essential for uptake of B Co[60] that it and rat intrinsic factor be present together whereas in Herbert's experiments the uptake of B Co[60] was greatest when the rat intestine was exposed first to hog intrinsic factor and then to B Co[60] —Ed]

Interrelationship between Ascorbic Acid and Cyanocobalamin Mueller and co workers found that the rate of disappearance from the plasma of ascorbic acid injected intravenously was increased in pernicious anemia and that in contrast the levels of the plasma dehydroascorbic acid rose unduly These abnormalities disappeared after vitamin B_{12} therapy To determine whether there was a relation between vitamin B_{12} and ascorbic acid as suggested by such observations E V Cox R Gaddie D Matthews W T Cooke and J J Meynell[6] (Birmingham England) studied the effect of B_{12} administration on plasma concentrations of ascorbic acid before and after intravenous injection of 250 mg sodium ascorbate in patients with low serum B_{12} levels pernicious anemia adult celiac disease and regional ileitis These patients had significantly lower resting plasma ascorbic acid levels than normal persons on a similar intake of ascorbic acid and the rate of disappearance of the injected sodium ascorbate was increased

After B_{12} therapy the abnormal ascorbic acid metabolism was corrected in pernicious anemia and improved in adult celiac disease No change was noted in regional ileitis The effect in pernicious anemia and in adult celiac disease was masked in patients partaking of either a plentiful or a grossly deficient supply of ascorbic acid in the diet In regional ileitis the lack of effect of B_{12} was attributed to the activity of the underlying disease A significant correlation was noted between levels of seromucoid a nonspecific measure of disease activity and resting plasma ascorbic acid

Patients with pernicious anemia in relapse had a signifi

(6) Cl S 12 681 69 November 1958

min B_{12} by liver slices in vitro Grasbeck and Nyberg thereafter found that oral administration of the calcium chelating agent ethylenediamine tetra acetic acid (EDTA) inhibited the uptake of vitamin B_{12} by normal subjects Consequently the present authors postulate that deficiency of free calcium ions in the intestine is apparently one cause of the poor vitamin B_{12} absorption in steatorrhea This is not the sole cause because 2 patients did not respond fully even though calcium was given Other factors may be decreased production of intrinsic factor rapid passage of the chyme decreased absorptive area envelopment of the vitamin by fat droplets in the chyme abnormal microbial flora and various combinations of these factors

Calcium ions are removed by the fatty acids as insoluble calcium soaps This is thought to be the cause of poor calcium absorption in steatorrhea Because calcium ions are probably necessary for the intestinal absorption of vitamin B_{12} this may also be the cause of vitamin B_{12} deficiency in steatorrhea

► [In extension of his work with B Co^{60} uptake by liver slices in vitro Herbert (J Clin Invest 38 102 1959) has shown that calcium ions are similarly essential to the action of hog intrinsic factor on rat intestinal mucosa —Ed]

Effect of Intrinsic Factor on Vitamin B_{12} Uptake by Rat Intestine In Vitro Recently the rat has been useful as an experimental animal in studying B_{12} absorption Previous attempts to use segments of intestine in vitro have been unsatisfactory Elliott W Strauss and T Hastings Wilson[6] (Boston) applied the everted sac technic to this problem They found that rat gastric juice markedly stimulates intestinal uptake of B_{12}

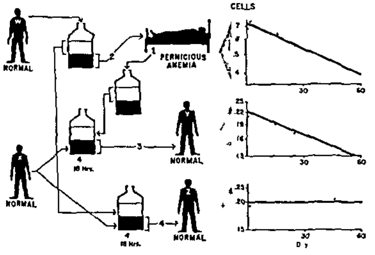
METHOD —Segments of washed intestine were everted filled with fluid and tied at both ends The solution on the serosal side was bicarbonate saline glucose The filled sac was placed in a 50 ml Erlenmeyer flask containing bicarbonate saline neutralized gastric juice and Co^{60} labeled B_{12} After incubation the tissue was digested and radioactivity counted in a well type scintillation counter

Gastric guice stimulated B_{12} uptake into the gut wall by a factor of 11 fold compared with the control Concentration of B_{12} in the intestinal wall was more than twice that in the final mucosal solution Although both fluid and glucose moved across the full thickness of the tissue no B_{12} appeared on the serosal side of the intestinal sac The midportion of

(5) P oc Soc Exp B l & M d 99 24 6 O t be 1958

persons as well as in the individual patients themselves These facts suggest the presence of a hemolytic factor in the disease

Experiments conducted by the authors indicate that a *hemolytic factor destroys normal erythrocytes transfused to a* patient with untreated pernicious anemia and that the plasma of untreated patients with pernicious anemia has a factor or a deficit capable of injuring normal erythrocytes



F g 54—Comp so f tes f l f f b m l rythrocyt t ed pe ou em pl m d rm l pl m bseq tly t f ed to rm l ec p ent N mal ryth ocyte t f sed t p t t w th t eated pern ciou em d l ed ll t d pern mia pl sm d t y d t dom nd cated b l pe f pl t ed cu f ect d ggl t nabl cell ou t (p tw rve) N rm l c ll st l rm l pl m d b qu tly t s f sed t mal cip t b rm l rv l d cat d by h rizo tal curve f co ected ggl t bl ll t (C rt y f H m lton H E t l J Lab & Cl Med. 51 942 955 J 1958)

Blood group compatible normal cells stored at 4 C with pernicious anemia plasma for 14 hours and thereafter at room temperature for 4 hours are destroyed at random when transfused to a normal subject The rates of loss are similar to those of normal cell destroyed in patients with untreated pernicious anemia and of pernicious anemia cell in normal persons (Fig 54) It is *unlikely that the manipulations of the* blood in incubation were responsible for these injuries because cells from the same donor handled in just the same way but incubated in normal plasma survived normally

cantly faster rate of disappearance of ascorbic acid than after B_1 induced remission the rate in remission did not differ significantly from the rate in normal subjects (Fig 53) The effect of B_1 deficiency on ascorbic acid metabolism was greater when the deficiency was associated with a megaloblastic anemia in pernicious anemia and celiac disease than when there was normal erythropoiesis

In pernicious anemia B_{12} appears to act slowly and thus more as a sparing agent than by preventing the immediate destruction of ascorbic acid Though a similar effect is observed in adult celiac disease some further disorder of as

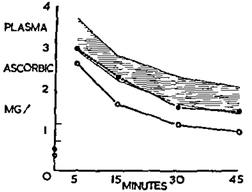


Fig 53—M l f t a n a c b t t t n p t ts w th p rn c ou a em a r l p (tl c le) d v t m B nd d em s ( ] d le) Sh ded a epr ent mean] ± tw the ct d st da d r f t t n n rmal s bjects (Co te y f Cox E V t l Cl n S 17 681 69 N mber 1958)

corbic acid metabolism appears to exist even in the B_1 saturated state The nature of the association of B_1 deficiency and the abnormality of ascorbic acid metabolism is not clear although Lester Smith suggests that because in one reducing enzyme system vitamin B_1 is a prosthetic group it may so act on ascorbic acid

Studies with Inagglutinable Erythrocyte Counts VII *Further Investigation of Hemolytic Mechanism in Untreated Pernicious Anemia and Demonstration of Hemolytic Property in Plasma* Henry E Hamilton Raymond F Sheets and Elmer L DeGowin[7] (State Univ of Iowa) point out that erythrocytes from persons with untreated pernicious anemia have short survival times when transfused to normal

(7) J Lab & Cl Med 51 94 955 J 19 8

of factors other than vitamin B_{12}—both known and unknown—deficiency of which might give rise to spinal cord disease e g thiamine or nicotinic acid In both patients the neurologic picture did not deteriorate after institution of vitamin B_{12} parenterally as highly purified liver extract In the second patient the neurologic symptoms developed during treatment with folic acid alone Malabsorption of radioactive cobalt labeled vitamin B_{12} was demonstrated in this patient

The authors suggest that the term subacute combined degeneration of the spinal cord be discarded because (1) the disease usually begins insidiously and not subacutely (2) the combination of lesions in the posterior and lateral tracts is frequently absent (3) the name is cumbersome and (4) it does not take into account the fact that peripheral neuritis develops first and is usually associated with degeneration in the cord and that a few patients shows mental changes due to brain damage

► [A clarifying demonstration of the high degree of correlation between vitamin B deficiency and degenerative disease of the spinal cord of the type seen commonly but not exclusively in pernicious anemia The diagnostic value of serum vitamin B levels in such atypical patients has been emphasized by Victor and Lear (Am J Med 20 896 1956) and the neurologic hazards of therapy with folic acid without parenteral vitamin B by Vilter et al (Blood 5 695 1950) There is no need to urge that irrespective of the presence of typical macrocytic anemia or megaloblastic marrow when there is doubt a neurologic disorder resembling subacute combined degeneration of the spinal cord should be treated empirically with parenteral vitamin B —Ed]

Some Physicochemical Properties of Vitamin B_{12} Binding Substances of Normal and Chronic Myelogenous Leukemic Serums are described by Aaron Miller and John F Sullivan[9] (Boston Univ) The serum in chronic myelogenous leukemia has an increased concentration of vitamin B_{12} and an increased capacity to bind vitamin B_{12} as measured in vivo or in vitro By microbiologic assay of the electrophoretically separated fractions of normal and chronic myelogenous leukemia serums vitamin B_{12} was found bound to the alpha$_1$ and alpha globulins The same proteins were also involved in the in vitro binding of added vitamin B_{12} When cobalt[60] labeled vitamin B_{12} ($B_{12}Co^{60}$) sufficient to saturate normal serum is added in vitro it is bound chiefly to the beta and alpha globulins as measured by dialysis technics In contrast the high levels of added $B_{12}Co^{60}$ bound by

(9) J Lab & Cl Med 53 607 616 Ap 1 1959

No clue was found as to the nature of the destructive factor or deficit in pernicious anemia other than the speculation that the red cells are injured by contact with pernicious anemia plasma in such a way that the normal erythrocytes so treated are destroyed at random in a normal person The results appear to exclude the function of some abnormal tissue in the pernicious anemia patient as the only cause for destruction of red cells These studies do not differentiate between an acquired defect of the pernicious anemia cells and a development defect which shortens their survival time

The slow disappearance curves describing the hemolysis of tagged normal cells in patients with untreated pernicious anemia can be differentiated from the rapid disappearance curves due to isoimmunization

► [Next please what is the injurious factor in the plasma? Can we speculatively combine the observations of the authors of the preceding article indicating a possible lack of reducing activity for ascorbic acid in pernicious anemia and the evidence of Beutler *et al* (J Lab & Clin Med 45 286 1955) that red cells lacking in reduced glutathione activity are susceptible to lysis by oxidant drugs?—Ed]

Subacute Combined Degeneration of Spinal Cord in Nonaddisonian Megaloblastic Anemia was studied by John Richmond and Stanley Davidson[8] (Univ of Edinburgh) Review of the literature revealed that subacute combined degeneration of the spinal cord may develop in vitamin B_{12} deficiency states other than addisonian pernicious anemia Investigation of reports relating to neurologic features that may occur in diseases of the intestinal tract disclosed 10 examples of subacute combined degeneration of the spinal cord 5 caused by structural disorders of the intestine and 5 by idiopathic steatorrhea In only 1 of these patients was histologic proof of this degeneration obtained

The authors observed 2 men aged 43 and 45 in whom macrocytic anemia (known to be caused by megaloblastic blood formation in the first patient) was associated with an intestinal disorder Histologic examination of the spinal cord at autopsy revealed demyelinization of the posterior and lateral columns in the first patient and of the posterior columns in the second The changes in the second patient were very similar to the *ascending degeneration that follows injury* to the cells in the posterior root ganglions

Patients with intestinal disease may have malabsorption

(8) Q rt J Med 7 517 531 O t be 1958

molecular weight thus nondiffusible through cellophane and nonassimilable by micro organisms It is possible that simple proteolysis in the stomach in which the bound protein attached to the vitamin is degraded into a peptide allows the free form to be simply absorbed by diffusion through the gut wall This hypothesis would account for inconsistencies in the action of intrinsic factor preparations by variation in the molecular size of the bound protein components Good evidence for this hypothesis would be obtained if a peptide derived not from an animal intestinal (intrinsic) source but from a mold or bacterial (extrinsic) source promoted oral absorption of vitamin B_{12} (as the complex) in patients with pernicious anemia and in small doses maintained such patients in health

Active vitamin B_{12} peptide complex was derived from a streptomyces The cobalamin peptide was released from the protein complexes within the cells and concentrated and purified by ion exchange chromatography counter current solvent extraction activated carbon treatment and ammonium sulfate precipitation A red precipitate was finally obtained Paper chromatography and paper electrophoresis showed only 1 vitamin B_{12} peptide complex Acid hydrolysis yielded a mixture of aminoacids glutamic aspartic glycine alanine valine proline serine threonine arginine cystine (or cysteine) leucine isoleucine phenylalanine lysine and histidine Methionine and hydroxyproline were not detected

The current view on the cause of pernicious anemia is that absorption of extrinsic factor (crystalline vitamin B_{12}) is facilitated by combining with the intrinsic factor If true treatment with intrinsic factor together with a relatively small dose (30-45 μg) of vitamin B_{12} should be successful Although several such preparations are marketed results have been disappointing The true cause of pernicious anemia may be even more fundamental—failure of simple proteolysis in the stomach This view returns to the original concept of pernicious anemia proposed by Castle in 1929 that it was due to virtual deficiency brought about even in the presence of a diet adequate for the normal person by defective gastric digestion of protein as a result of the achylia gastrica On this theory extrinsic and intrinsic factors are no longer necessary nor is the third factor of Castle because this free

chronic myelogenous leukemia serum is found on the alpha₁ and alpha globulins

The authors investigated the nature of the substances in normal and leukemia serums that bind B_{12} Co^{60} and some physicochemical characteristics of this binding reaction Added B_{12} Co^{60} was rapidly bound and once bound did not exchange with additional carrier vitamin B_{12} in both normal and leukemia serums Of the bound B_{12} Co^{60} of normal serums i e the B_{12} Co^{60} nondialyzable at pH 7 5 60 77% was measured as free by Euglena gracilis assay whereas *only 9 13% was so measured in chronic myelogenous leukemia serums* At the acid pH at which the E gracilis assay i performed (pH 3 6) 47-48% of the bound B_{12} Co^{60} of normal serums became dialyzable compared to 11 12% in leukemia serums The binding of B_{12} Co^{60} by normal serums was unaffected by pH levels above 4 5 but a marked decline in binding was found at pH 3 6 In contrast at pH 3 6 B_{12} Co^{60} binding by chronic myelogenous leukemia serums was unaffected Preheating of normal serums to 69 73 C for 3 minutes decreased B_{12} Co^{60} binding by 49-64% compared to 10 19% in leukemia serums The binding of B_{12} Co^{60} *by the seromucoid fraction of normal serum was equal to an* average of 0 26 mμg /ml constituting 13% of the total serum binding whereas binding by the chronic myelogenous leukemia seromucoid was equal to 7 74 mμg /ml constituting 61% of the total serum binding Binding by the leukemia seromucoid was not affected by acidification or heating to 100 C

Differences noted between normal and chronic myelogenous leukemia serums with respect to (1) effects of acidification and heating on B_{12} Co^{60} binding and (2) availability of bound B_{12} Co^{60} for E gracilis are due to the increased binding by the leukemia seromucoid The increased in vitro binding ability of leukemia serums for added B_{12} Co^{60} is due to the increased B_{12} Co^{60} binding by the seromucoid fraction of serum the increased in vivo binding capacity of leukemia serums for vitamin B_{12} may be attributed to a similar mechanism

Oral Treatment of Pernicious Anemia *New Approach is* described by J G Heathcote and F S Mooney [1] Most forms of vitamin B_{12} available as food are bound to proteins of high

(1) Lancet 1 98 987 May 10 1958

confirmed by its distribution coefficient between benzyl alcohol and water Latner's observation that the vitamin B was not bound to peptide consequently further work seemed pointless—Ed.]

Absorption of Orally Administered Vitamin B_1 in Pernicious Anemia *is still not well understood* It is generally accepted that efficiency of absorption [of native vitamin B_1 in food or as such in doses of less than 5 µg—Ed] depends on adequate gastric secretion of intrinsic factor and in pernicious anemia *deficient absorption is the result of defective* gastric secretory function Some patients apparently become refractory to intrinsic factor of heterologous origin Heathcote and Mooney have suggested that intrinsic factor as normally *considered does not exist and that vitamin B_1 peptide* complex is better absorbed than is vitamin B_1 This view has been criticized on the grounds that the hematologic responses produced by the vitamin B_1 peptide complex might *have occurred with pure vitamin B_1 alone in similar dosage* [The initial daily dose of vitamin B_1 peptide used contained 100 µg vitamin B_1 —Ed]

In short term 15 day trials with a daily dose of 50 µg vitamin B_1 *alone Chalmers and Hall reported hematologic* responses in 6 consecutive patients with pernicious anemia Similarly Estren and Wasserman treated 8 such patients with daily oral doses of 5 16 8 µg only 1 failed to respond *It has also been claimed that d sorbitol increases absorption* of orally administered vitamin B_1 in normal subjects but there is no evidence that this happens in patients with pernicious anemia

J N Marshall Chalmers and N K Shinton[2] (Birmingham England) studied 21 patients with pernicious anemia in relapse who were given daily oral doses of 20 500 µg vitamin B_1 for 15 days to 50 months Of 13 whose daily oral dose was 20 200 µg 10 showed variable but sometimes remarkable hematologic improvement In 1 who did not respond by the 15th day response was delayed (Fig 55) Daily oral dose was 100 µg in this patient but a reticulocyte peak was not noted until the 21st day and the serum vitamin B_{12} level was not normal until the 35th day Two others who did not respond could not be continued on oral therapy long enough

All 8 patients treated with daily oral doses of 500 µg showed uniformly successful and prompt hematologic re

(2) La t 2 1 98-150 Dec 0 1958

form of the vitamin will be of suitable size for simple ab sorption in the small intestine

Of 6 patients newly diagnosed as having pernicious anemia who were treated exclusively with vitamin B_1 peptide complex most received 100 µg vitamin B_1 daily for 8 days then 50 µg daily for 14 days and thereafter 10 µg daily in the form of the vitamin B_{1} peptide complex All showed good hematologic and clinical response for periods from 140 to 290 days Reticulocyte crisis with maximums of 11 17% developed at about the end of the 1st week in every patient

Vitamin B_1 peptide complex is the most effective oral preparation yet described because the ratio of peptide to vitamin is only 6 8 1 Such vitamin B_1 peptide could be produced in the stomach by simple proteolysis Intrinsic factor probably does not exist

► (Although the subtitle and some of the claims made in this article scarcely seem justified in the light of previous work it has attracted much attention Nevertheless within a year after their initial observations on the subject Castle *et al* (Am J M Sc 180 305 1930) reported that hog pepsin was inactive as intrinsic factor with beef muscle in pernicious anemia In 1936 Flood and West (Proc Soc Exper Biol & Med 34 542 1936) found that exposure of gastric juice to pH 10 destroyed its peptic but not its intrinsic factor activity Four years later Formijne (A M A Arch Int Med 66 1191 1940) showed that the active principle of a beef muscle extract was dialyzable but that incubation of the extract with gastric juice produced an active mixture but not an active dialyzable material such as a peptide would have been

Doses of vitamin B alone similar to those used by Heathcote and Mooney in the form of their vitamin B peptide (100 µg then 50 µg daily) may well have produced according to the next article the effects seen by them in pernicious anemia Moreover as pointed out by Latner (Lancet 2 961 Nov 1 1958) the available commercial preparation of the alleged vitamin B peptide is not in fact such but rather a mixture of vitamin B with some peptide and some protein Even if this were an artifact of the mild analytic procedure he used he noted that dissociation of such a peptide would inevitably occur in the pernicious anemia intestine before absorption

It is an interesting commentary on the times that despite the several letters exchanged by Heathcote and Mooney and their critics in the columns of the *Lancet* no one has yet published the essential direct clinical evidence as to whether or not their peptide is more active than its content of vitamin B alone *in the same pernicious anemia patient* This is perhaps attributable to the circumstance that such an observation cannot be carried out by the current and convenient use of radioactive vitamin B When we attempted to use the old fashioned method of serial reticulocyte responses (Minot and Castle Lancet 2 319 Aug 10 1935) the first pernicious anemia patient responded initially with a modest reticulocytosis to 5 µg vitamin B alone daily and not again in a second 10 day period when the vitamin B peptide was given In a second patient given only 2 5 µg vitamin B daily no reticulocyte responses appeared until in a third 10 day period when the vitamin B peptide was administered together with a purified preparation of hog intrinsic factor By that time we had

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(2) Lancet 2 1298 130 Dec 20 1958

sponse and a striking increase in the serum vitamin B_{12} level to normal by the 10th day

Of 3 patients given 50 µg for 50, 21 and 22 months all had normal hematologic values within 2 months but none maintained a satisfactory serum vitamin B_{12} level throughout the trial

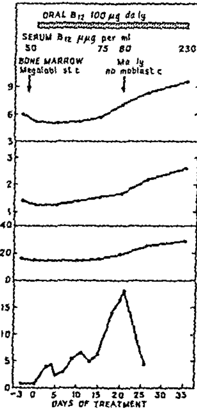


Fig 55 — D layed e por t da l al d s of 100 µg t m n B e tn m t 60 (C u tesy of Ch lme s J N M nd Shi t N K Lan et 2 1 98 130 D 0 19 5)

out the trial All remained in excellent health but 1 showed a slight fall in hemoglobin and red blood cell count by the 45th month of treatment Three patients receiving 100 µg 2 receiving 200 µg and 4 receiving 500 µg oral vitamin B_{12} for 6-26 months reached and maintained normal serum vitamin B_{12} values

Eight patients were followed after changing from oral

to intramuscular maintenance therapy In only 1 who was taking 50 µg vitamin B_1 daily orally was there any material difference in serum vitamin B_1 values

These observations corroborate the view of other that use of extraneous sources of intrinsic factor or of additive thought to enhance absorption of the vitamin in complex form is not essential for absorption of oral vitamin B_1 [in pharmacologic doses—Ed] in patients with pernicious anemia Vitamin B_1 given alone in 100 µg daily dosage is absorbed and in adequate amounts is effective in maintenance therapy There is evidence of more rapid absorption with progressive increase in dosage from 20 to 500 µg daily so that absorption i possibly achieved by mass action leading to diffusion through the intestinal wall There may be more than one mechanism for the intestinal absorption of vitamin B_1

Parenteral therapy is still the most reliable method for insuring against relapse in pernicious anemia but with the close co operation of the patient oral treatment taken daily may be effective

[Ross *et al* (Blood 9 473 1954) and Dosch rholmen and Hagen (J Clin Invest 36 15 1 1957) have demon trated from studies of plasma radioactivity the delayed absorption of small amounts (0 56 µg) of B Co^{60} with intrinsic factor in contrast to the rapid absorption of larger doses (50 100 µg) of B Co^{60} alone —Ed]

Radioactive Vitamin B_1 Tests in Pernicious Anemia after Oral Maintenance Therapy Jorgen Pedersen and Ingrid Lbbesen[3] (Copenhagen) observed that most patients with pernicious anemia who are treated for some time with oral preparations of vitamin B_1 and hog intrinsic factor do not absorb vitamin B_1 well even though additional hog intrinsic factor is added Diagnosis was established in each of 23 patient by low level of vitamin B_1 in the serum megaloblastic erythropoiesis anemia hi tamine refractory achlorhydr a and initial response to injection of vitamin B_1 Five patients had in addition latent steatorrhea A Schilling test was performed on each Treatment before the test consisted of an initial injection only in 6 oral maintenance therapy after an initial injection in 13 4 had no prior treatment

The percentage excretion of radioactive vitamin B_1 in Schilling tests without intrinsic factor varied from 0 0 to 7 2 It was statistically higher before treatment in patients with

(3) A a m d sc d 161 413 4 5 1958

partial and lower in those with total megaloblastic erythropoiesis Of the 10 patients who had received no oral treatment 8 showed excretion typical of pernicious anemia Patients treated orally for the preceding 6 84 months had abnormally low percentage excretions with or without intrinsic factor

Of the 13 patients who were previously on oral preparations 11 had abnormally low excretion in the Schilling test with added intrinsic factor 9 had abnormally low serum levels of vitamin B_1 and 5 had abnormal bone marrow All with abnormal bone marrow had abnormally low vitamin B_1 levels and abnormally low percentage excretion after added intrinsic factor preparation Those with normal bone marrow had normal or low levels of B_1 greater excretion in the Schilling test and normal as well as abnormal levels of excretion with added intrinsic factor In general patients who were insufficiently treated by oral preparations as judged by the marrow picture had the lowest vitamin B_1 level in the serum and the lowest percentage excretion in the Schilling test with and without added intrinsic factor

Many patients with pernicious anemia who are treated with oral preparations of vitamin B_1 and hog pyloric mucosa for some months will show the malabsorption pattern in the Schilling test and will not respond to an intrinsic factor preparation from hog pyloric mucosa Intestinal malabsorption per se therefore cannot be distinguished from acquired intolerance hog intrinsic factor by tests with such a preparation in patients who have been on such oral therapy Oral maintenance therapy combining vitamin B_1 and hog pyloric mucosa should be abandoned unless controlled closely by plasma vitamin B_1 level and sternal marrow examination

Intrinsic Factor Inhibiting Substance in Serum of Orally Treated Patients with Pernicious Anemia A new type of oral preparation consisting of purified hog pyloric mucosa plus vitamin B_1 has recently become popular Only 100 mg hog pyloric mucosa causes substantial absorption of vitamin B_1 in pernicious anemia and usually produces complete remission initially In prolonged treatment however many patients relapse and several have shown myelopathy even without hematologic relapse in the peripheral blood

These oral preparations fail because intestinal absorption

of the combination is blocked Human intrinsic factor action is not blocked The block may be due to some sort of sensitization and recently antibodies against intrinsic factor have been developed By immunization of rabbits with intrinsic factor preparations from man and from pig pylorus the serum of treated rabbits was found to contain a substance capable of inhibiting human and pig intrinsic factor activity respectively in pernicious anemia

Michael Schwartz[4] (Copenhagen) studied the serum from healthy persons and from four groups of patients with typical pernicious anemia (1) untreated (2) treated 1 5 years with oral preparations of vitamin B_{12} plus hog pyloric mucosa (3) treated orally with a crude stomach prepara

URINARY EXCRETION IN SCHILLING TEST PERFORMED WITH 50 ML SERUM FROM PATIENTS WITH PERNICIOUS ANEMIA TREATED ORALLY WITH CRUDE STOMACH PREPARATION*

	I sl FA	
No	100 Mg H g Pyl n M	100 Mg H g Pyl c M + 50 Ml S um
0 5	15 7	1 4
0	14 0	1 4
0	14 0	2 2
0	16 4	12 9
0	20 7	10 6
0	14 0	18 4

F g a per e tag f dm t d v t m B C ted u ı 24 hou

tion and (4) treated by injection To test for the presence of antibody 50 ml serum was used in patients with pernicious anemia known to show typical responses in the Schilling test to administration of 0 5 ug vitamin B_1 Co^{60} with and without intrinsic factor

Serum from healthy persons and patients with untreated pernicious anemia contained no substance which inhibited intrinsic factor Of 21 patients treated with oral preparations of vitamin P_1 and hog intrinsic factor for 1 year or more 16 had inhibitory activity in the serum and in some this inhibition was almost complete The usual Schilling test using hog pyloric mucosa when applied to 13 of these patients whose serums had been tested showed absorption to be blocked in each Serum from 6 patients treated orally with crude stomach preparations showed gross inhibitory activity in 3 (table) Intestinal absorption by the usual

(4) La cet 2 61 6 J ly 12 1958

Schilling test was normal in 5 reduced in 1 On the contrary serum from 2 patients treated with injections showed no intrinsic factor inhibiting activity

In some cases the experiments were repeated with the same serum mixing radiocobalt B_{12} and hog pyloric mucosa for 10 minutes before adding the serum The intrinsic factor inhibiting activity was unaltered by this procedure probably indicating that it is directed against the vitamin B_{12} plus intrinsic factor Three serums known to inhibit hog pyloric mucosa activity were tested in the same way using human fundus mucosa as intrinsic factor In 2 inhibiting activity against this homologous intrinsic factor was pronounced

As intestinal absorption of vitamin B_{12} proved to be normal in some cases with inhibiting activity in the serum and as the intrinsic factor inhibiting activity was shown to operate also against human intrinsic factor such activity is probably not the sole cause of the intestinal blockade following long continued oral treatment of pernicious anemia

► [However if an antibody was present against intrinsic factor this need not necessarily be species specific —Ed]

Effect of Pteroylglutamic Acid Administration on Serum Vitamin B_{12} Concentration in Pernicious Anemia in Relapse Because parenteral vitamin B_{12} is effective in pernicious anemia the clinical manifestations of this disease are generally believed to be due to deficiency of this vitamin Serum concentration of vitamin B_{12} is low Factors of the folic acid group also have hemopoietic activity in this disease but administration of pteroylglutamic acid may provoke the nervous system lesions of vitamin B_{12} deficiency

J Bok J G Faber J A de Vries W F Stenfert Kroese and H O Nieweg[5] (Univ of Groningen) gave pteroylglutamic acid to 13 patients with pernicious anemia and studied the effect on serum concentration of vitamin B_{12} Serum vitamin B_{12} levels were within the usual range for pernicious anemia 17 100 μμg /ml and hemoglobin above 6 Gm /100 ml Pteroylglutamic acid was given orally 15 mg daily for 5 days to 10 patients for 4 days to 1 patient for 6 days to 1 and for 8 days to 1 Total vitamin B_{12} activity of the serum was determined before and on the last day of pteroylglutamic acid administration by bioassay with Lactobacillus leichmannii

(5) J Lab & Clin Med 51 66 671 May 1958

No nervous system disturbances were produced Serum vitamin B_1 levels fell in 10 of the 13 patients (table) In 1 patient the vitamin B_1 content was below 17 $\mu\mu g$ before pteroylglutamic acid was given and further decrease could not be detected by the method used In 2 patients no reticulocyte response occurred and the vitamin B_1 level remained unchanged In all other patients studied significant hemopoietic response was produced by pteroylglutamic acid

The effect of pteroylglutamic acid on blood formation seems related to decrease in the serum vitamin B_1 Probably decrease in the vitamin B_1 level is due to the hemopoi

EFFECT OF PTEROYLGLUTAMIC ACID ON VITAMIN B LEVEL AND RETICULOCYTE COUNT IN PERNICIOUS ANEMIA IN RELAPSE*

CASE NO	DO ES PGA (15 MG EACH)	VIT B BEFORE PGA	VIT B AFTER PGA	D CREASE OF VIT B_{12} (PER CENT)	RETICULOCYTE RESP NSE
1		50	3	30	
	4	100			
3	6	50	30	40	
4	5	83	6	19	
5	5	63	39	38	
6		9		19	
7		33	<1	>48	
8	5	88	<1	>81	
9	5	60	30	0	
10	8	83	<1	>9	
11	5	<1	<17	0	
1	5	50	50	0	
13	5	50	50	0	

S t eq t t tm t w th t m B ult d n g od h mop t po se

etic activity of pteroylglutamic acid Available data are consistent with the theory that vitamin B_1 and folic acid act as coenzymes at different stages in the same synthetic process essential for blood formation and that both are concerned with the synthesis of nucleic acids

Administration of pteroylglutamic acid to patients with pernicious anemia in relapse may produce a change in the distribution of the vitamin B_1 supply correlated with increase of blood formation Presumably more vitamin B_1 is required by the bone marrow when hemopoiesis is accelerated The rapid development of nervous system lesions sometimes associated with exclusive pteroylglutamic acid administration in vitamin B_1 deficient subject may be due to decrease in the amount of B_1 available for the nervous system

Schilling test was normal in 5 reduced in 1 On the contrary serum from 2 patients treated with injections showed no intrinsic factor inhibiting activity

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(5) J Lab & Cl Med 51 66 6 3 May 1958

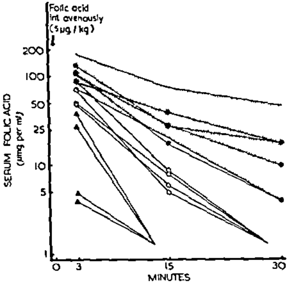


Fig 56 —Se m f l d c ntrat ft r ject f 15 μg /kg l p t t w th vit m n B den ncy I 4 p t t t l d ll nt x d d 3 000 000/ mm (●) n 4 th nt wa 1 800 000 000 000 (○) n 4 th cou t wa l th n 1 700 000 (▲) St ppl d p t g f l e n m l bjects (C rte y f Ch I et l B t J H m t 4 435 446 O t b 1958)

not occur in patients with pernicious anemia until such de ficiency develops It is impossible to say whether the deficiency in these patients is as severe as that in patients with uncomplicated folic acid deficiency However although the clearance rate is similar in the two group patient with primary vitamin B_1 deficiency respond to treatment with B_1 without added folic acid Further preliminary observa tions suggest that much smaller amounts of folic acid are needed to restore the clearance rate to normal in patients with B_1 deficiency

► [Recently Herbert *et al* (Fed Proc 18 246 1959) pre ented evidence that serum levels of folic ac d as determined by growth of Lactobacillus casei show excellent correlation with cl nical e idence of megaloblastic anemia due to fol c acid deficiency —Ed]

Folic Acid Studies in Megaloblastic Anemia Due to Prim idone The megaloblastic anemia that develops in patients while receiving barbiturate like anticonvulsants resembles folic acid deficiency because serum vitamin B_1 concentra

Clearance from Plasma of Folic Acid Injected Intravenously in Normal Subjects and Patients with Megaloblastic Anemia I Chanarin D L Mollin and B B Anderson[6] (Postgrad Med School London) injected folic acid 15 µg/kg intravenously into normal subjects and patients with megaloblastic anemia and studied the plasma folic acid clearance by measuring serum folic acid concentrations 3 15 and 30 minutes after injection

In normal subjects there was rapid clearance of most of the injected dose from the plasma Mean serum folic acid concentration 3 minutes after injection was about equivalent to a mean total plasma content of 40% of the injected dose About 60% of the dose had therefore been cleared into the tissues and extracellular fluids in the first 3 minutes after injection Subsequently the serum folic acid concentration fell more slowly a detectable amount still being present in the plasma 30 minutes after the injection

The folic acid clearance was more rapid than normal in all except 1 of the 8 patients with megaloblastic anemia associated with idiopathic steatorrhea in all the patients with vitamin B_{12} deficiency who had red cell counts of less than 2 000 000 cu mm (Fig 56) in all the 4 patients with megaloblastic anemia associated with pregnancy in 3 of 7 patients with iron deficiency anemia in all 7 of those with leukemia and related disorders and in 1 patient with megaloblastic anemia due to treatment with phenytoin sodium

Clearance was normal in 1 patient with mild megaloblastic anemia associated with idiopathic steatorrhea in those with vitamin B_{12} deficiency who had only slight or moderate degrees of anemia and in those with megaloblastic anemia due to treatment with primidone and barbiturates

The increased demand for folic acid which manifests itself by rapid clearance from the plasma of folic acid injected intravenously probably indicates an abnormal degree of folic acid unsaturation of the tissues and a folic acid deficiency state As in some of the iron deficiency anemia patients folic acid deficiency may be incidental Normal clearance probably excludes significant folic acid deficiency but more evidence is required to confirm this

Whatever the actual cause of the folic acid deficiency these results suggest that a severe megaloblastic anemia does

(6) Brit J Haemat 4 435 446 Oct 1958

Children with acute leukemia who had received no amethopterin for at least 1 week before study excreted 0-1.18 µM/hour. Three who had never received the drug excreted 0-0.03 µM/hour. *In* 16 patients *receiving* amethopterin excretion was in excess of 1.27 µM/hour and 11 excreted over 8 µM/hour. The rise in excretion was not apparent until after several weeks of amethopterin therapy and often *not until long after remission of the leukemia had begun*.

The increased excretion in patients treated with amethopterin is presumably due to interference by the drug with the formation of tetrahydrofolic acid. If the increase in urinary formiminoglutamic acid and formic acid can be considered an index of folic acid deficiency, these observations may provide in vivo support for the thesis that leukemic cells have a greatly increased sensitivity to folic acid deprivation.

► [When applied to the clinical detection of folic acid deficiency in megaloblastic anemias the results of the enzymatic method have been irregular and some patients with vitamin B deficiency have given positive results. Clarification may be expected as a result of correlative studies of folic acid levels in the serum by the Lactobacillus casei method.—Ed.]

Bone Marrow Failure Due to Relative Nutritional Deficiency in Cooley's Hemolytic Anemia. Painful Erythropoietic Crises in Response to Folic Acid were observed by James H. Jandl and Mortimer S. Greenberg[9] (Boston).

Woman, 36, had lifelong symptoms of mild or moderate fatigue, dyspnea on exertion and slight icterus. Since childhood she had splenomegaly and anemia. Except for three episodes of exacerbation with normal pregnancies, the anemia had been chronic, stable and of only moderate severity. On three *subsequent occasions*, at about 18-month intervals, this woman, who was believed to have mild Cooley's anemia (homozygous classic thalassemia), had subacute exacerbations of the anemia. Each episode was associated with bone marrow failure as manifested by reticulocytopenia and diminished icterus. No precipitating *illnesses were involved*, and there were no morphologic changes in peripheral blood or marrow other than those of thalassemia. There was no hematolgic response to withdrawal from the home environment or to parenteral administration of vitamin B_{12} or of pyridoxine. Each time, however, there were striking hematologic responses to large doses (18.3 mg. daily) of folic acid (Fig. *57*). These responses involved diffuse, intense bone pain and tenderness, particularly of the lower spine, pelvis and femora, an increase in early erythroid precursors in the bone marrow, a striking increase in reticulocyte level and a rapid return of the red cell count to the usual level.

Although the efficacy of folic (pteroylglutamic) acid in correcting this patient's episodes of bone marrow failure was

(9) New England J Med 60 461 468 Mar 5 19

tions are normal and there is no response or only suboptimal response to vitamin B_{12} whereas response to folic acid is excellent

I Chanarin P C Elmes and D L Mollin[7] (Postgrad Med School London) report a case

Woman 44 had typical symptoms signs and laboratory finding of folic acid deficiency while taking primidone She had severe anemia and megaloblastic marrow Absorption of vitamin B_{12} and serum levels of B_{12} were normal Folic acid injections of 30 mg or more daily induced a reticulocyte response with a peak of 49% on the 5th day Studies showed oral absorption of folic acid to be normal Clearance studies showed that folic acid was cleared from the plasma at a normal rate before treatment was started on the day following treatment and on the 9th day after receiving large dose of folic acid This clearance rate was unlike the rapid clearance found in patients with megaloblastic anemia due to folic acid deficiency [See preceding article —Ed]

The megaloblastic anemia resembles that seen in pregnancy and in certain patients with intestinal malabsorption syndrome but the results of these studies suggest that the cause is different Patients in whom megaloblastic anemia develops due to these barbiturate like anticonvulsants apparently have no deficiency in tissue stores of folic acid The anemia is thus probably not due to folic acid deficiency but to interference by the anticonvulsant drug with the action of available folic acid in cellular metabolism Withdrawal of primidone relieves the anemia

The action of folic acid in treatment is analogous to the action of folic or folinic acid in reversing the megaloblastic change in patients being treated with folic acid antagonists

Urinary Excretion of Formiminoglutamic Acid by Human Subjects after Antifolic Acid Therapy Formiminoglutamic acid is an intermediate in histidine metabolism and requires tetrahydrofolic folinic acid for its further metabolism Urinary excretion is markedly increased in folic acid deficient rat Using the enzymatic procedure of Tabor and Wyngarden for the assay of formiminoglutamic acid Howard H Hiatt Madeline Goldstein and Herbert Tabor[8] found small amounts in the urine of adults and children with a marked elevation in excretion after amethopterin (methotrexate) therapy in children with acute leukemia

Urinary excretion of formiminoglutamic acid in children who did not have leukemia varied from 0 to 0 51 μM /hour

(7) Brit M J 2 908 July 1958
(8) J Clin Invest 37 983 June 1958

a relative deficiency state must be postulated The term rel ative deficiency is intended to indicate that in certain in stances of increased red cell turnover in chronic hemolytic anemias supranormal or pharmacologic amounts of an erythropoietic metabolite may be necessary for optimal cel lular growth

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HYPOCHROMIC ANEMIAS

Iron Enzymes in Iron Deficiency II Catalase in Hu man Erythrocytes Contrary to previous opinions iron en zymes are not inviolate in iron deficiency In rat the cyto chrome C content of the liver and kidneys becomes mark edly diminished

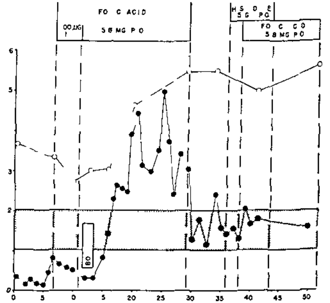
Ernest Beutler and Richard K Blaisdell[1] (Univ of Chi cago) have extended their investigations to the catalase sys tem in man using the method of von Euler and measuring the amount of peroxide remaining at 3 6 and 9 minutes by titrating an aliquot with permanganate after the reac tion had been stopped with sulfuric acid The catalase activ ity per milliliter of red cells was essentially the same in nor mal and iron deficient subjects regardless of the severity of the anemia as indicated by the hemoglobin level No signifi cant sex difference was noted

Apparently even in conditions of severe iron need cata lase concentration in human red cells remains normal If it is true that catalase and hemoglobin derive their heme groups from a common source apparently the catalase synthesizing mechanism is more successful in competing for the limited amount of available heme than is the hemoglobin synthesiz ing mechanism This would appear to be the reverse of the situation with cytochrome C in animals deficient in iron the hemoglobin returns to normal while the cytochrome C content of the liver and kidney is still abnormally low

Iron Metabolism in Patients after Partial Gastrectomy Subtotal gastrectomy is followed by iron deficiency anemia with incidence as high as 50% Alexander R Stevens Jr Giacomo Pirzio Biroli Henry N Harkins Lloyd M Nyhus and Clement A Finch (Univ of Washington) measured

(1) J Cl I L 37 833 835 J 1958
(2) A n S g 149 534 538 April 1959

well established none of the usual criteria for true folic acid *deficiency were fulfilled* (1) there were no morphologic al terations of red or white cell precursors such as those that usually accompany this condition (2) there was no thera peutic effect from daily injection of 400 µg folic acid an amount that usually is sufficient to correct simple folic acid deficiency and probably approximates the maximum daily



F g 57—E yth po t n f m ph m l g d of f l c acid d r g d ep d , ft f l t sp d t phy log d (C t sy f J ndl H and G e b rg M S N w E gl d J M d 260 461 468 Mar 5 1959)

assimilation of folic acid from dietary sources (3) urinary excretion of folic acid was normal before therapy and in creased normally after injection of small or large doses of folic acid and (4) the abnormal urinary metabolite formi minoglutamic acid which appears in folic acid deficiency states was not excreted [see preceding article—Ed] The patient s diet was above average in foods rich in folic acid and there was no evidence of intestinal malabsorption

To reconcile the consistent therapeutic efficacy of folic acid in this patient with absence of morphologic or biochem ical evidence of true deficiency of folic acid the existence of

year In the authors 5 gastrectomized patients who were not bleeding the rate of development of anemia did not exceed these values and therefore is consistent with malabsorption of iron superimposed on already exhausted iron stores

► [This is a valuable contribution However as some previous studies have failed to show that achlorhydria predisposes to decreased food iron absorption the mechanism of production of iron deficiency after subtotal gastrectomy is not necessarily due to reduction of acid secretion —Ed]

Studies in Iron Transportation and Metabolism XI Critical Analysis of Mucosal Block by Large Doses of Inorganic Iron in Human Subjects The mucosal block mechanism as a prime regulator of iron absorption has become widely accepted though the original observations were made on a surprisingly small number of dogs but it fails to explain the excessive absorption and heavy tissue iron deposits found in some subjects after prolonged ingestion of large amounts of dietary or medicinal iron or the increased absorption of iron from the diet by patients with idiopathic hemochromatosis Confusion has resulted from application of the term mucosal block to several different situations Care must be taken to avoid assuming that the effect of large doses of orally administered iron in depressing absorption of a tracer dose given several hours later is the same as the depressing effect on absorption caused by heavy tissue stores decreased erythropoiesis or the prolonged oral administration of moderate doses

Elmer B Brown Jr Reubenia Dubach and Carl V Moore[3] (Washington Univ) studied the blocking effect of large oral doses of iron in man Each subject took an unblocked (control) test dose of radioactive iron and in a second study a comparable dose of radioiron 3 or more hours after a large blocking dose of inert iron

Findings were not uniform varying considerably from subject to subject and at different times in the same person In general the results showed that (1) 2 or 4 mg/kg iron given several hours before a 5 mg tracer dose of radioiron tended to decrease absorption of the tracer dose (2) the block persisted for about 6 hours in normal subjects but for only 3 hours in patients with iron deficiency (3) ferric chloride tended to decrease absorption of the tracer dose less than did ferrous sulfate and (4) oral ascorbic acid did not consistently

(3) J Lab & Clin Med 52 335 355 Sept mb 1958

the iron stores absorption and excretion of iron in 8 patients after partial gastrectomy The patients fell into two groups 3 women showed normal or slightly depressed hematocrit values normal to elevated plasma iron concentrations some what elevated red cell volumes and normal iron stores on bone marrow aspiration These patients were considered to have normal iron metabolism

The second group was composed of 3 women and 2 men all of whom had some degree of anemia microcytosis hypo ferremia and decreased marrow iron All responded to oral iron therapy These patients therefore fulfilled the criteria for iron deficiency anemia

Absorption of iron was determined at the time of the ini tial blood studies by administration of a known amount of radioactive iron Fe^{5} with a standard meal containing 5 mg total iron and simultaneous intravenous injection of a known amount of the second iron isotope Fe^{59} Absorption was calculated from the amount of those two isotopes ap pearing in the blood at 2 weeks as compared with the amounts administered The per cent absorption in postgas trectomy patients with normal iron stores and with iron de ficiency was compared with that of control subjects with normal and with depleted body iron respectively Absorp tion was so low in both normal and postgastrectomy pa tients (averages 6 and 49% respectively with adequate iron stores as to make comparison difficult However the in creased iron absorption characteristic of simple iron defi ciency (average 21 6%) was not seen in the postgastrectomy patients with iron deficiency (average 3%)

The rate of loss of body iron was determined from the fall in circulating red cell radioiron during 1 year The data in 5 of 7 postgastrectomy subjects were similar to values ob tained in normal men and averaged 20% decrease The 2 pa tients clearly exhibiting increased radioiron loss were known to be losing blood for reasons unrelated to peptic ulcerative disease

Recent studies indicate that in the normal man or nonmen struating woman the total daily loss of iron exclusive of blood loss is 0 6 mg /day The greatest degree of anemia which may develop through normal iron loss and defective iron ab orption is equivalent to a fall of about 2 Gm hemo glob n/100 ml circulating blood or 5 points of hematocrit/

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Absorption of Inorganic Iron from Graded Doses Its Significance in Relation to Iron Absorption Tests and Mucosal Block Theory are evaluated by Mary D Smith and I M Pannacciulli[4] (Postgrad Med School London) Absorption of inorganic iron is conveniently studied by using radioactive iron to label an oral test dose and subsequently estimate the amount eliminated in the feces The unrecovered portion can be assumed to have been absorbed and in normal and iron deficient subjects it can be checked by estimating the amount of radioactivity ultimately appearing in the hemoglobin

The authors determined the size of the oral dose from which maximum percentage absorption occurs and investigated whether any level of oral intake above which the total amount of iron absorbed is not augmented whatever the increase in the dose Graded doses of iron from 0 001 to 300 mg labeled with tracer dose of Fe^{59} were given by mouth as ferrous sulfate solution to subjects without anemia and to patients with iron deficiency anemia The amount absorbed was calculated from fecal estimations Mean absorption in those without anemia decreased from 33% of the 0 001 mg dose to 12 6% of the 100-mg dose (Table 1) and in iron deficient patients from 50% to 37 5% respectively (Table 2) No limit to the total amount absorbed was reached the total absorbed from the 100 mg dose increasing to 12 6 mg and 37 5 mg in those without anemia and in the iron deficient group respectively Further increase occurred after 300 mg was given

As a test dose 5 10 mg iron given to a fasting subject was found most suitable Variability in absorption limits the value of the test but hematologically normal subjects as a group appear to absorb less absolutely and on a percentage basis than patients who are anemic from chronic blood loss Results indicated that mucosal control on absorption of soluble inorganic iron is slight and does not limit absorption to body requirements

Granick has demonstrated ferritin in the intestinal mucosa after administration of iron by mouth and his suggestion that its formation provides control on the absorption of iron has gained wide acceptance (mucosal block theory) The increasing total absorption in iron deficient sub

(4) B t. J H m t 4 4 8 434 O t be 1958

reduce the block The nature of the blocking effect was not discovered Saturation of plasma transferrin did not seem important

An attempt was made in a normal subject to saturate the plasma iron binding capacity artificially by intravenous injection of saccharated iron oxide If plasma transferrin were completely saturated with iron it was reasoned that it could not accept iron from the intestinal mucosal cell and that the iron in the process of absorption might accumulate in the mucosal cell and block absorption of more iron Actually though the iron binding capacity was acutely and completely saturated during the experimental period no block to iron absorption occurred

The studies establish the fact that a block to iron absorption can be produced in human beings by administration of moderately large doses of iron salts several hours before the tracer dose The block is never complete The conditions responsible for a block of absorption are artificial and unlikely to be found in man except when iron salts are taken medicinally or under unusual circumstances when large amounts of iron are found in beverages or in food (as among Bantus from cooking in iron pots) Ordinarily dietary iron is so small (12 20 mg /day) that it is insufficient to produce the kind of block observed in these experiments When therapeutic iron has been taken any block which does occur is not great enough to prevent accumulation of abnormally large amounts of iron in the body The degree of block to iron absorption demonstrated in normal subjects in these experiments is inadequate to prevent absorption of unneeded iron from the diet Large amounts of iron may be absorbed and stored by the patient who is anemic but not iron deficient and who may be taking iron medicinally for a prolonged period in a vain attempt to cure the anemia Indiscriminate iron therapy is dangerous The safeguard provided by a supposed mucosal block has been overestimated Experimental evidence does not justify the current use of the term mucosal block to describe the physiologic regulation of iron absorption Until the factors which control iron absorption are more clearly understood the phrase should be abandoned

► [An important clarification of a matter that had become a legend —Ed]

OTHER ANEMIAS

Changes in Iron Metabolism in Early Chloramphenicol Toxicity Chloramphenicol may cause all degrees of hemo poietic depression from fatal aplastic anemia to minimal marrow depression readily reversible on removal of the drug Frank marrow hypoplasia is easily recognized As this advanced stage bears a high mortality rate early detection before irreversible changes occur is desirable David Rubin Austin S Weisberger Robert E Botti and John P Storaasli[5] (Cleveland) present a method of early detection of erythro poietic depression due to chloramphenicol with use of fer rokinetic technics

METHOD —Ten μc of Fe^{59} is incubated for 20 30 minutes under sterile conditions with 20 ml of the subjects heparinized plasma and given intravenously Plasma radioactivity is determined for the next 2-4 hours and then the radioactivity appearing in the circulat ing erythrocytes is determined daily

In 10 of 15 patients receiving chloramphenicol such ferro kinetic studies were normal or compatible with the under lying disease The other 5 showed evidence of depression of erythrocyte production attributable to chloramphenicol They had received 1 4 Gm daily for 7 21 days They showed a marked delay in disappearance of radioactive iron from the plasma with one half times of disappearance ranging from 130 to over 240 minutes instead of the normal 50 100 min utes Eight or more days after chloramphenicol therapy was stopped plasma disappearance of Fe^{59} was normal During this same period no significant amounts of radioactivity ap peared in the circulating erythrocytes within 24-48 hours When chloramphenicol was stopped radioactivity appeared in the erythrocytes and a reticulocyte response was noted (Fig 58) Two patients were not anemic when depressed red cell production was detected but showed a subsequent fall in hematocrit values during the period of toxicity and nonproduction

One of the 5 patients with erythropoietic depression had leukopenia thrombocytopenia and hypoplasia of the bone marrow The other 4 had no discernible abnormality of

(5) J Clin I 37 1 86-1 9 S pt mbe 19 8

jects given high doses of iron fits in with this theory because the total amount assimilated never exceeds the amount needed for complete hemoglobin regeneration but from results observed in normal subjects it is difficult to accept the

TABLE 1 —ABSORPTION OF IRON FROM DOSES OF 0 001 TO 100 MG IN PATIENTS WITHOUT ANEMIA

No of s lj ts	H m gl b (g /100 l)	S m o (g /100 ml)	Dose of (mg)	I b pt (Mc) (±SE)	(mg)
1	12 3 16	6 145	0 001	24 7±5 43	0 0003
19	3 5– 6	6 190	0 1	33 1±4 59	0 033
19	2 5 6	63 45	1 0	29 8±3 87	0 30
22	12 5 13 7	68 190	5	20 0±2 82	1
12	11 7 14 9	51 160	10 0	17 8±4 9	1 8
10	13 2– 6 0	97 –160	2 0	15 1±2 85	3 0
3	13 2 4 8	5 * 11	50 0	16 3±2 4	8 2
17	13 5 4 8	9 129	100 0	12 6±1 75	12 6

★Two the t m t ons o the bjects w (0 μg and 73 μg /100 ml re pect ly

TABLE 2 —ABSORPTION OF IRON FROM DOSES OF 0 001 TO 100 MG IN PATIENTS WITH IRON DEFICIENCY ANEMIA

No f s bj ct	H (l l (g / 00 l)	S (μg /100 ml)	D f o (mg)	I b pt (M) ( )	( )
	8 5 2 0	4 25	001	50	0 0005
	6 1 12 0	0– 5	0 1	13	0
3	0–1 0	11 5	1 0	53	53
7	5 0– 2 0	0–25	5 0	56	8
	5 0– 8 9	1 20	1 0	5	5
1	8 9	0	2 0	65	3 0
1	8)	0	5 0	35	17 5
2	6 1	0–16	100 0	37 5	3 5

concept that a mucosal mechanism can prevent accumulation of iron in the body in excess of its needs

There is no reason to believe that the system does not operate efficiently when tissues are depleted of iron as in iron deficiency anemia or that it can be brought to a standstill when tissues are saturated though there is some reduction in the proportion handled when the dose of iron is large

► [The data in the tables are useful and show why in practice substantial therapeutic effects can be obtained in iron deficiency anemia with daily doses of exsiccated ferrous sulfate as small as 300 mg containing about 100 mg iron Taking the authors figure of 37 5 mg iron absorbed daily this if converted to hemoglobin would give a daily gain of 0 22 Gm hemoglobin/100 cc in a 5 liter blood volume

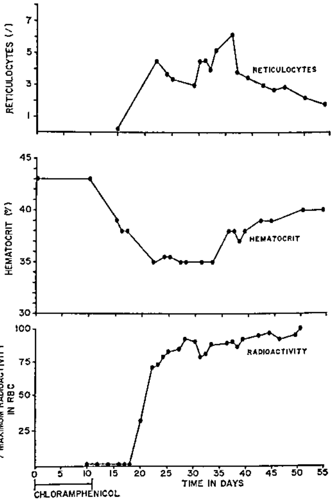
For further analysis of the mucosal block theory see the preceding article —Ed]

plasma iron binding globulin was found to be abnormally highly saturated with iron With recovery from toxicity saturation decreased Thus determination of the plasma iron pattern is a simple means of detecting erythropoietic depression Early detection may prevent more serious consequences of aplastic anemia due to drugs toxic to the bone marrow

Refractory Normoblastic Anemia Clinical and Hematologic Study of Seven Cases is presented by J V Dacie Mary D Smith J C White and D L Mollin[6] (Postgrad Med School London) Refractory anemia denotes an anemia without any *recognizable underlying systemic or hematologic disease* and which proves resistant to all forms of therapy Refractory anemia has been subdivided into two groups according to whether sternal marrow aspiration revealed normo or megaloblastic erythropoiesis Subsequent discovery of folic acid has shown that almost all or perhaps all of the patients falling into the megaloblastic group respond at least partially to treatment with this vitamin The normoblastic group however remains unexplained and poorly described Cases of this type though rare were probably identical with some of the cases of so called pseudoaplastic anemia More recently it has been suggested that some example at least of refractory anemia are in reality chronic forms of erythremic myelosis (erythroleukemia or di Guglielmo s syndrome)

The authors studied 7 patients with refractory anemia of unknown origin Their bone marrows were intensely cellular because of erythroid hyperplasia Cells with large nuclei were often noted and a few resembled intermediate megaloblasts (Fig 59) Dying and degenerating forms were conspicuous The cytoplasm of many of the basophilic and polychromatic normoblasts was abnormal it was scanty in amount appeared thin and was often vacuolated with little evidence of hemoglobin formation The nuclei of such cells were often pyknotic and when the cytoplasm was basophilic the cells somewhat resembled lymphocytes When stained for ionized iron most of the normoblasts could be seen to contain gross excess of large siderotic granules (Fig 60) In 1 patient there were definite and in several other patients possible megaloblastic changes which could be corrected

(6) Brit J Haemat 5 568 January 1959



F g 58—Eff ct f chlo mph n col on h matoc t val t locyt a d ap pe an of F n d c ll (Co rt y of Rub n D *et al* J Cl n I e t 37 1286 1 9 S pt mber 1958)

leukocytes or thrombocytes and bone marrows showed nor mal or increased cellularity

Abnormalities of ferrokinetics were delay in the disap pearance of Fe^{59} from the plasma appearance of radioac tivity in the reticuloendothelial system rather than in the bone marrow and failure of radioactivity to appear in the circulating red cells for 8 or more days Coincidentally the

plasma iron binding globulin was found to be abnormally highly saturated with iron With recovery from toxicity saturation decreased Thus determination of the plasma iron pattern is a simple means of detecting erythropoietic depression Early detection may prevent more serious consequences of aplastic anemia due to drugs toxic to the bone marrow

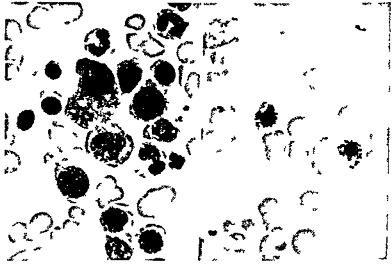
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(6) B t I II m t 5 56 8 J ry 1959

by administration of folic acid Basically however the type of hyperplasia can only be described as normoblastic

All had some degree of leukopenia and 2 had mild thrombocytopenia The life span of the patients own red cells was slightly diminished in 3 of the patients in whom this was studied but although hemolysis thus contributed to their anemia it was clearly only a minor factor A feature in common was the finding of many excessively large siderotic



F g 59 (l ft) —St n l bo m w f m w m 58 May G w ll G m t ed c d f m ×825
F g 60 (ght) —St l b m w f om same p t t w th P l s t f d d d f m ×1100
(Co t sy f Dac e J V *t al* B t J Haemat 5 56 82 J n ary 1959)

granules in many of the normoblasts and presence in the peripheral blood of varying numbers of hypochromic cells among a population of orthochromic cells The patients thus appear to have a defect of erythropoiesis and possibly of leukopoiesis and thrombopoiesis also associated to varying degree with a defect in the synthesis of hemoglobin

These patients suffer from a profound disorder of growth and differentiation of erythropoietic cells of unknown origin and apparently irreversible but without morphologic evidence of leukemia Basically there appears to be a disturbance of the growth of erythropoietic tissue amounting to impaired maturation associated with hyperplasia This could

be due to lack of an essential metabolite Dietary origin with or without failure of absorption seems unlikely It is possible that refractory normoblastic anemia is a very chronic form of erythremic myelosis Although there is no positive evidence that it is a deficiency disease secondary deficiencies of hemopoietic factors such a folic acid and also perhaps pyridoxine may accompany it and complicate the clinical and hematologic pictures

► [This critical and extensive evaluation by Dacie *et al* deserves careful study in the original See also the last article under Perniciou and Other Nutritional Macrocytic Anemias by Jandl and Greenberg —Ed]

Thymoma and Pancytopenia Report of Case and Review of the Literature are presented by John W Josse and Sumner I Zacks (Massachusetts Gen l Hosp)

Woman 73 was admitted because of headaches of 7 days duration At age 68 she had chronic glossitis inflammation necrosis and oral culture of Candida albicans At age 70 glossitis had progressed and the fingernails were destroyed White cell count was 4 000 with 26% neutrophils Chest x ray study showed a soft tissue mass in the anterior mediastinum The anemia progressed to 8 6 Gm /100 ml hemoglobin white cell count decreased to 2 700 with 11% neutrophils and the platelets were decreased Reticulocytes were persistently below 1% Bone marrow biopsy and imprints showed striking hypoplasia of all elements No megakaryocytes were present Serum electrophoresis showed relative increase in gamma globulin Red cell survival tests measured with Cr [1] were normal but Fe [9] turnover was extremely low taking 323 minutes to clear half the i otope activity from the plasma as compared with a normal of 70 140 minutes These data indicated markedly impaired erythropoiesi with no evidence of hemolysis

Blood transfusions then prednisone produced only temporary improvement Furunculosis that developed in the skin of the buttocks responded to local measures and systemic treatment with chloramphenicol and erythromycin Acute bacteremia with I eudomonas aeruginosa developed and the patient died At no time did she show definite evidence of myasthenia gravis

At autopsy two mas es were found in the anterior mediastinum a large colloidal thyroid gland and a large thymic tumor Sections of rib and vertebral marrow showed many fat cell between which were moderate number of plasma cells many lymphocytes mature red cells brown pigmented macrophages and infrequent immature myeloid cells

Thirteen cases reputed to represent coexistence of primary thymic tumor and blood dyscrasia have been reported The patients (9 women 4 men) were aged 44 77 Hemoglobin ranged from 3 to 10 8 Gm /100 ml and white cell counts from 650 to 10 450 Only 2 patients had low platelet counts

(7) N w E gl d J M d 259 113 117 J ly 17 1958

Bone marrow was reported as hypoplastic in 3 whereas only the erythroid series was depressed in 10 The spleen was enlarged in 4 All 13 patients had a thymoma but only 1 had symptoms of myasthenia gravis Four patients were cured by thymectomy alone or in conjunction with splenectomy or steroid therapy Five others had no effect from thymectomy and in 4 thymectomy was not done

The association of isolated anemia and thymoma is unlikely to be mere chance

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SPLENIC FUNCTION AND HYPERSPLENISM

Normal Functions of Spleen Relative to Red Blood Cells Review According to William H Crosby[8] (Walter Reed Army Med Center) *erythropoiesis* is a function of the spleen only during the first 5 months of intrauterine life when certain fixed mesenchymal cells in the spleen give rise to so called hemocytoblasts which in turn produce erythroblasts

There are three ways in which the spleen might conceivably exert control over erythropoiesis (1) It might hasten or impede the enzymatic synthesis of hemoglobin or stromal proteins Though this is a possibility there is no evidence to suggest it (2) It might increase or decrease the number of erythropoietic units in the bone marrow Hemolytic disease induced by the spleen can cause an erythroid hyperplasia of the marrow which is not control of erythropoiesis (3) It might determine the age at which the young erythrocytes are released from the bone marrow When the young red blood cell has lost its nucleus it pauses as a reticulocyte to wait its turn to go into the circulation The reticulocyte stage of a red cell s development may last 2 days Normally perhaps half of this time is spent waiting in the marrow When this is so the peripheral reticulocyte count reflects only the last day of the reticulocytes existence If the cells were to leave the marrow 1 day earlier they would live 2 days in circulation and the peripheral reticulocyte count would be doubled yet the output of the marrow would not have increased This phenomenon is sometimes observed in pa

(8) Blood 14 399 408 April 1959

tients in whom splenectomy fails to cure a hemolytic anemia

A splenic effect on maturation of the red cell s surface can be demonstrated by splenectomy After splenectomy the sur face area of the red cells is larger than before but the cellular volume is normal which means that the cells are thinner They appear on stained smears as thin target cells The change is not abrupt Loss of the spleen does not increase the surface area of the cells already present but by the process of normal attrition and replacement a population of thin cells appears Reticulocytes are slightly sticky and this may determine when they leave the marrow [Jandl (J Clin In vest 37 905 1958) has confirmed Berendes observation that reticulocytes are normally concentrated in the spleen prob ably until no longer sticky He suggests that this explains the apparent effect of splenectomy on marrow function — Ed]

The reservoir function of the spleen refers to the seques tration of red cells in the pulp and splenic sinuses This is not an important function of the human spleen as it is in some animals The culling function of the spleen refers to its ability to scrutinize the passing red cells and remove from circulation those which do not meet certain minimum re quirements such as congenital spherocytes The role of the spleen in iron metabolism is related to its destruction of red cells Hemoglobin from the red cells is degraded and the iron is returned to the erythroblasts to be reused Organs other than the spleen are sometimes involved in hemoglobin breakdown but do not as readily dispose of the iron The pitting function of the spleen refers to its ability to remove a solid particle from the cytoplasm of a red cell without de stroying the cell itself The rapid removal of transfused siderocytes by the spleen and their persistence in splenec tomized subjects is an illustration The final normal func tion of the spleen relative to erythrocytes is to destroy them when they reach the end of a normal life cycle

Outcome of Neutropenic Splenomegaly Treated Surgi cally Immediate results of splenectomy in neutropenic splenomegaly are excellent with disappearance of patho logic signs improvement in the general condition and ap parent cure This assessment however *may be premature* according to R Poinso E Hawthorn J N Bondil P Mar

Bone marrow was reported as hypoplastic in 3 whereas *only the erythroid series* was depressed in 10 The spleen was enlarged in 4 All 13 patients had a thymoma but only 1 had symptoms of myasthenia gravis Four patients were cured by thymectomy alone or in conjunction with splenectomy or steroid therapy Five others had no effect *from thymectomy and in 4 thymectomy was not done*

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(8) Blood 14 399-408 April 1959

taining to autoantibodies also detract from the primary role of the spleen and support the idea of a more general disturbance of the entire reticuloendothelial system

If the spleen dominates the clinical picture in neutropenic splenomegaly it is because it is the organ which contains the most reticuloendothelial tissue but it is far from being the only one From the practical standpoint however splenectomy still remains a remarkable treatment If the liver is not too greatly injured this operation causes regression of the changes in the reticuloendothelial system Even when the liver is severely involved the disease is arrested and stabilized for a time Irradiation may have the same effect demonstrated by the 14-year survival of Pieri s patient

► [The widely accepted conclusions that the spleen may become an over active filter for red cells white cells or platelets makes the problem comprehensible The anemia leukopenia and thrombocytopenia of Laennec s cirrhosis are thought to be the result of congestive splenomegaly due to intrahepatic vascular constriction Although this may be a latent and only slowly progressive process it will not be affected by splenectomy and it subsequent overt development as here is not surprising The other condition sometimes unobtrusively underlying splenic neutropenia is some form of leukemia or lymphoma which will also later become apparent —Ed]

POLYCYTHEMIAS

Anemia and Polycythemia in Uniovular Twins The simultaneous occurrence of anemia and polycythemia in newborn monozygotic twins was observed by Margaret M Kerr[1] (Glasgow Royal Maternity and Women s Hosp Glasgow) on four occasions The hematologic data are summarized in the table

CASE 1 —Gravida III delivered twin boys spontaneously She was known to be Rh negative The first twin delivered looked plethoric for several days Results of the examination of the cord blood showed a negative Coombs test and a remarkably high hemoglobin level Complete blood examination confirmed the polycythemia but there was no excess of reticulocytes and the blood film was normal The second twin was pale the spleen tip was palpable and the liver enlarged Examination of the peripheral blood revealed severe anemia with a reticulocytosis and many erythroblasts Since the mother was known to be Rh negative erythroblasto is fetalis was the presumptive diagnosis The Coombs test on the cord blood was however persistently negative Half of the single placenta was grossly congested

(1) B r M J 1 90 903 Ap 4 1959

riq and R Bassilana[9] (Marseille) In a patient they observed regularly for a prolonged period hepatomegaly appeared 2½ years after operation They collected reports of 49 cases in which splenectomy or irradiation had been carried out but only 8 had been followed as long as 2½ years In a case reported by Pieri death occurred 14 years after the first irradiation and autopsy disclosed fatty degeneration of the liver

Among the 49 cases reviewed the liver was not mentioned at the time the disease was discovered in 9 it was normal in 23 and pathologic in 17 In 4 of the 17 histologic examination showed advanced cirrhosis chronic hepatitis with steatosis mild cirrhosis with marked steatosis, and limited areas of steatosis with pronounced diffuse hyperplasia of Kupffer cells In all but 1 case the hepatic condition was improved by splenectomy and in this case death occurred 6 days postoperatively The authors patient had a normal liver at onset but considerable hepatomegaly was first noted 2½ years after splenectomy Unfortunately liver biopsy was not done when the spleen was removed Puncture biopsy of the liver 3 years after splenectomy showed parenchymatous change consisting of localized steatosis and diffuse Kupffer cell hyperplasia Six months later the liver was further enlarged

Despite the absence of reports of other cases comparable to this case and that of Pieri the authors believe the dogma regarding cure of neutropenic splenomegaly after splenectomy should be revised since the liver is susceptible to late change The spleen is not the sole cause of the condition Both liver and spleen form part of the vast reticuloendothelial system and neutropenic splenomegaly may be an expression of hyperreticulism rather than hypersplenism Stimulation and hyperplasia of the reticuloendothelial system result in hypertrophy of the parenchyma of the liver and spleen Certainly involvement of the hepatic reticuloendothelial system determines the late prognosis after splenectomy If the system is slightly affected splenectomy may result in regression of hepatic lesions If it is considerably involved progression such as that seen in the authors case and that of Pieri probably occur Unfortunately late results of splenectomy are not reported in most cases Recent discoveries per

(9) S m e h p Ia s 34 84 ?90 O t 4 1958

present to produce the condition It may be postulated that there was some obstruction to the return of the blood to the placenta from the plethoric infant or obstruction of entry of blood in the anemic one This would agree with the placental findings—the engorged placenta of the anemic twin and the absence of engorgement in the placenta of the polycythemic one The nature of this obstruction is not easy to determine However the condition probably exists for some hours at least in utero because of the presence of the reticulocytosis in the anemic twin (table) More detailed study of the placentas might provide further information The syndrome especially in a mild form is probably more common than is realized

Cranium en Brosse in Polycythemia Secondary to Chronic Hypoxemia Antonio Ascenzi and Vittorio Marinozzi (Univ of Rome) describe 2 cases of congenital cardiopathy with cyanosis and polycythemia in which there were changes in the cranial vault similar to those observed in Cooley's anemia The recent literature contains reports of similar bony changes in congenital spherocytic anemia sicklemia polycythemia and malaria

CASE 1 —Girl 3½ was operated on for a heart lesion diagnosed as tetralogy of Fallot and died some hours later in anoxia Autopsy revealed that the bone marrow was almost completely hemopoietic Chronic stimulation of red cell production due to hypoxemia was evidenced by an increase in volume of the marrow at the expense of osseous tissue This explained the rarefaction of the osseous tissue in general and the thickening of the cranial vault in particular (Fig 61) Absence of the external table and extension of marrow to the periosteum indicated that the compensatory polycythemia had not reached the necessary level since the volume of the marrow continued to increase impeding formation of cortical bone

CASE 2 —Girl 6 with tetralogy of Fallot died 2 weeks after a Blalock operation Generally at this age the hemopoietic marrow does not occupy the entire medullary space of the skeleton Hence in this case the conditions permitted an adequate compensatory medullary hyperplasia without increase beyond the normal total volume of the marrow or consequently of the bony cavities This could explain the fact that the external table of the cranial vault was already partly reconstructed and that the trabeculae and medullary spaces did not show the completely characteristic en brosse appearance

These 2 cases express different phases of adaptation of the cranial skeleton to medullary hyperplasia Since this is found also in thalassemia it is believed that hyperplasia of the bone

( ) Acta h m 19 5 6 Ap May 1958

PERIPHERAL BLOOD VALUES IN PRESENT SERIES

Case	Weight (g)	Peripheral Blood				
		Sex	Hemoglobin (Gm /100 Ml)	Red Cell Count (Mill /Cu Mm)	Reticulocytes %	Film
1	5 0	M	21 8	8 66	2 3	Occasional erythroblasts
	2 690		7 7	2 20	19 0	Very numerous erythroblasts
	1 4 0	F	0 0	5 57	2 2	Occasional erythroblast
	1 080		8 3	2 28	13 0	Numerous erythroblasts
3	3 30	F	19	4 61	3 5	No abnormality
	2 190		14 1	4 42	7 3	
4	2 410	F	14 7	4 3	—	—
	490		1 8	7 00		—

with tortuous vessels whereas the other half was pale with collapsed vessels

Presumably there must have been some direct communication between the circulations of these twins The occurrence of arteriovenous shunts in the placenta in uniovular twin pregnancies is well known However as anemic and polycythemic twins occur rarely some other fac must be

18 Gm/100 ml Only 4 of these 11 had blood volume determinations 1 had absolute secondary polycythemia 1 borderline absolute secondary polycythemia and 2 relative polycythemia In 3 of the other 7 patients the hemoglobin decreased to normal after operation suggesting a cause and effect relation with the tumor Postoperative values for hemoglobin were not recorded in the other 4

The mechanism of production of polycythemia in patient with these tumors is not known Neurologic conditions other than infratentorial vascular tumors have been described as being associated with polycythemia with a lesion affecting the mesodiencephalic region a common feature All the patient reported in the literature and all but one of the authors showed papilledema Some authors believe that pronounced increase in intraventricular pressure affects either a postulated erythropoietic center or the regulatory cente s for water balance or both Holmes and associates consider that the primary stimulus is relative anoxia cau ed by depression of the medullary centers for a prolonged period due to a slowly growing tumor

Polycythemia is considered absolute if the erythrocyte volume inferred from plasma dye studies or from the use of albumin tagged radioiodine exceeds 60 ml/kg Normal is 40 50 ml/kg Increased hemoglobin and hematocrit values and morphologic changes in the granulocytic cells with or without splenomegaly may be considered diagnostic of absolute polycythemia even though blood volume is not dete mined

Polycythemia vera with manifestations in the central nervous sytem especially papilledema must be considered in the differential diagnosis of these lesions It is often difficult to determine clinically whether the polycythemia vera has caused the papilledema or whether both are secondary to a tumor in the posterior fossa The presence of such a tumor should be excluded before it is assumed the papilledema results from polycythemia alone

Blood volume studies are necessary to document these cases accurately These tumors are an adequate cause of relative polycythemia

Phlebotomy usually improves patients with polycythemia vera and the papilledema sub ides unless the brain has been damaged by hemorrhage or thrombosis Patients who have

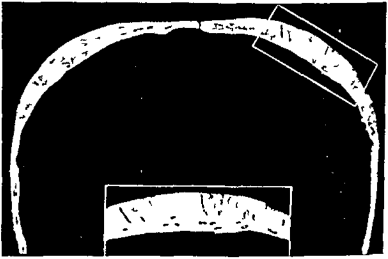


Fig 61 —Frontal section of calvarium in area of parietal bosses. Center inset shows enlarged portion of right frontal boss. (Courtesy of Ann. A... and Ma... no V. Acta haemat 19 253 26 Apr May 1958)

marrow constitutes the pathogenetic factor in the osseous lesion of Cooley's anemia. Systematic study of the skeleton in congenital cardiopathies with cyanosis and polycythemia might permit future determination of the frequency and factors which condition the bone changes particularly in the skull as a result of medullary hyperplasia

Polycythemia with Papilledema and Infratentorial Vascular Tumors Grier F Starr Charles F Stroebel Jr and Thomas P Kearns[3] reviewed the clinical records on the 106 infratentorial vascular tumors found in the surgical and autopsy files of the Mayo Clinic. Ninety seven involved the cerebellum 4 arose from the 4th ventricle 1 arose from the medulla 1 grew from the foramen magnum and 3 were merely designated infratentorial. Histologically 14 resembled cavernous hemangiomas and were considered congenital anomalies or hamartomas 90 were considered hemangioendotheliomas resembling capillary hemangiomas with endothelium lined spaces and varying amounts of stroma and 2 were classed as hemangioblastomas

Of the 106 patients 38 (36%) had hemoglobin values greater than 15 Gm/100 ml and 11 had values greater than

(3) Am J Med 48 978 986 May 1958

factors may have played a part The polycythemia can there fore be regarded as secondary to the renal tumor as main tained by previous authors A similar erythropoietic effect has been described for uterine myoma and cerebellar he mangioblastoma as well as benign renal adenoma and sev eral varieties of carcinoma

The mechanism for the erythrocytosis is unknown but probably an erythropoietic substance is produced perhaps in the tumor or in the neighboring renal parenchyma What ever the mechanism the fact remains that an appreci able percentage of patients with polycythemia have renal clear cell carcinoma The importance of careful abdominal palpation for a mass in the flank is obvious Abdominal radiography (a single flat film) to show renal outlines may be recommended in addition There can be no doubt of the necessity for urologic investigation of hematuria in polycy themia Hematuria gross or microscopic i e occasional to many red blood cells per high power field occurred in 20 patients with polycythemia vera among 183 in whom the urine was analyzed

Polycythemia in Primary Carcinoma of Liver A J S Mc Fadzean David Todd and K C Tsang[5] (Univ of Hong Kong) in 176 consecutive patients with primary hepatocar cinoma found 17 with red cell counts and hemoglobin levels significantly higher than those of healthy Chinese Red cell counts ranged from 6 100 000 to 7 700 000 and hemoglo bin levels from 16 6 to 19 4 Gm /100 ml compared with 5 080 000 ± 49 000 and 15 13 ± 0 6 Gm /100 ml respec tively in healthy controls and 3 690 000 ± 52 000 and 10 59 ± 1 77 Gm /100 ml in patients with uncomplicated cirrho sis of the liver The respective plasma and red cell volumes were 45 2 and 36 2 ml /kg in healthy controls 75 5 and 33 5 ml /kg in patients with uncomplicated cirrhosis of the liver and 68 8 and 46 ml /kg in those with hepatocarcinoma and cirrhosis Hemoglobin level in all patients with hepatocar cinoma was lower than in the healthy controls but higher than in patients with uncomplicated cirrhosis The red cell count and hematocrit did not differ significantly from those in healthy controls but were higher than in those with cir rho is alone The plasma volume of patients with hepatocar cinoma was greater than that in healthy controls but not

(5) Blood 13 4 7 435 M y 1958

cerebellar vascular tumors should not be significantly bene fited by this procedure

► [The authors remarks imply acceptance of the credo that the accu rate diagnosis of polycythemia requires that the circulating red cell volume be increased Granted that it usually is when the hematocrit is significantly so in the well hydrated patient with significant polycythemia one still wonders whether the more esoteric nature of the blood volume measurement compared to the hematocrit compensates for the greater un certainty of what is the normal red cell volume for a given patient The evidence points to regulation of erythropoiesis not by blood volume but by the oxygen transported by the arterial blood (Erslev A J Erythropoietic function in dilution anemia Blood 10 616 1955) What should we say of the pregnant woman whose red cell volume is increased by 10% but whose arterial hemoglobin concentration is decreased by 20%? Is she polycy themic or is she anemic? Certainly in physiologic terms she is probably neither for her increased cardiac output brings a normal amount of oxy gen in a given period of time to the peripheral tissues —Ed]

Polycythemia and Renal Carcinoma Report of Ten New Cases Two with Long Hematologic Remission Following Nephrectomy is presented by Albert Damon Donald A Holub Meyer M Melicow and Aurelio C Uson[4] (Columbia Univ) Coexistence of polycythemia and carcinoma of the kidney has been reported in at least 21 patients Although the first notation appeared in the American literature and 8 of the cases occurred in this country American observers have merely stated the fact of association Personal communica tions from several clinics suggest that the syndrome is more common than the relatively few published reports indicate

The authors observed 10 patients with polycythemia and renal carcinoma and reviewed data on 12 previously docu mented cases from the literature The syndome occurred in 4 4% of 205 patients with polycythemia and 2 6% of 350 pa tients with renal carcinoma seen in Presbyterian Hospital

The renal tumors as well as adjacent parenchymal tissues were not histologically unique in the six specimens studied The polycythemia was for the most part a simple erythro cytosis without pronounced splenomegaly leukocytosis or thrombocytosis It thus resembled secondary rather than primary polycythemia except that it did not depend on ar terial oxygen unsaturation Two of the authors patients had complete hematologic remission after nephrectomy 1 for 2 years and 1 for 11 years Two others from the literature had similar remissions for 14 months and 3 years Of the 22 pa tients thus far described all 8 who had nephrectomy had subsequent hematologic remission whether or not other

(increased hematocrit) because of dehydration (high hemoglobin concentration) and were later polycythemic (increased total blood volume) in an effort to compensate for the apparent dilution anemia? At any rate it is to be hoped that the authors will pursue their studies further in such a land of opportunity —Ed]

Therapy of Polycythemia Vera with Myleran® Myleran® has been used in the treatment of chronic granulocytic leukemia since 1953 Niel Wald Takashi Hoshino and Mary E Sears[6] (Atomic Bomb Casualty Commission Hiroshima) used the drug in 9 relapses in 5 cases of polycythemia vera regardless of the leukocyte level In each instance it induced a clinical and hematologic remission The average dose that produced full remission was 29 4 mg /week (range 22 40 mg) Only partial remissions resulted in 2 instances in which 14 and 17 mg /week were used In cases in which more than one fully effective course of Myleran® was given subsequent remissions were produced without significant dosage increase

Seven complete remissions were characterized by disappearance of clinical symptoms and of abnormal physical findings including hypertension and splenomegaly when present Hematologic improvement also occurred In the 2 incomplete remissions clinical improvement occurred but although leukocytes and platelets decreased red cell values showed little change When adequate dosage was given hemoglobin red blood cell and hematocrit levels were effectively decreased in each instance Studies of Cr^{51} survival times in 3 patients showed red cell survival to be shortened during remission

If further study proves Myleran® to be effective in treating polycythemia several advantages will accrue The need for P^{32} or x rays will be obviated thu eliminating agents which can be leukemogenic to treat a disease which already has an increased incidence of leukemia Myleran® is inexpensive easily admini tered by the patient s own physician and requires no special treatment training authorization or consultation other than routine blood counts at biweekly or weekly intervals It is particularly noteworthy for its safety and freedom from side effects

(6) Blood 13 757 76 A g t 1958

significantly different from that in the controls with cirrhosis Plasma volume was increased in all patients but the red cell volume was greater in patients with hepatocarcinoma than in controls with cirrhosis though it was not significantly different from that in the healthy controls

However when the findings in individual patients were tabulated 17 had total red cell volumes greater than normal The reticulocyte count and total serum bilirubin are elevated in cirrhosis of the liver among the Chinese in Hong Kong indicating that excessive hemolysis contributes to the development of anemia Among patients with hepatocarcinoma the reticulocyte count and total serum bilirubin were greater than in healthy controls but not significantly different from those in patients with only cirrhosis of the liver Fecal urobilinogen excretion and hemolytic index were greater than in the healthy controls but lower than in the controls with cirrhosis

The observations indicate a significant increase in the total red cell volume with hepatocarcinoma in a cirrhotic liver The higher content of red cells and of hemoglobin per unit volume of blood is attributable to the increase in total red cell volume alone The polycythemia which has been considered secondary to the hepatocarcinoma is an absolute polycythemia It differs from polycythemia vera and other forms of secondary polycythemia in that the plasma volume is significantly increased However this plasma volume expansion is probably attributable to the cirrhosis of the liver which precedes hepatocarcinoma

► [I *found this article difficult to follow It starts off impressively* with 10% of a series of 176 patients with primary hepatocarcinoma having been observed early in the course of their disease to have red cells and hemoglobin levels higher than those of healthy Chinese controls However when subsequent observations were made on 28 other (?) such patients most blood values were found to be in the anemic range Thus the average hemoglobin in the *erstwhile polycythemic hepatocarcinoma patients* was by then 13 1±2 54 Gm in the normal controls 15 13±0 6 Gm and in the patients with uncomplicated cirrhosis 10 59±1 77 Gm It then appeared that this polycythemia *is different from others in that the total plasma* volume was increased in all 28 patients The total red cell volume was also increased in 17 but at a time when the patients had become anemic *Here perhaps is the confusion referred to in the editorial comment preceding this one* Is it possible that the patients were originally polycythemic

generations The limited family evidence is compatible with the assumption that the leukocyte factors are inherited either as dominants or recessives

Cyclic Neutropenia in Father and Daughter is reported by Betty M Hahneman and Howard L Alt[8] (Chicago)

CASE 1—Man 29 was first seen at age 14 He had had furunculosis at age 6 weeks and bronchopneumonia at 18 months Since age 2 frequent streptococcic throat infections had occurred with ulceration of the oral and pharyngeal mucous membrane fever and irritability Boils on the skin were also reported during some of the episodes of mucous membrane lesions Physical examination revealed no enlargement of lymph nodes liver or spleen The gums were granular and swollen Cyclic neutropenia was observed every 21 days Bone marrow examination at the time when no neutrophils were seen in the peripheral blood revealed nearly complete absence of the neutrophilic granulocytic series Episodes of fever and oral ulcers gradually became milder and less frequent and ceased entirely at age 18 He was well while in the army for several years except for an abscess under the left side of the jaw which was drained Remission had persisted for 11 years

CASE 2—Girl 26 months daughter of Case 1 showed similar cyclic episodes At age 3 months she began to show fever melena and vomiting followed by a prolonged episode of diarrhea An abnormality of the white blood cell count was reported at that time Episodes of fever once or twice a month began at age 7 months The father believed that the cyclic episodes were similar to those he had had as a boy Physical examination revealed a well developed child weighing 26 lb Lymph nodes were not enlarged and liver and spleen were not palpable During observation episodes of severe neutropenia occurred every 14 days The serum drawn during the neutropenic phase was tested for agglutinins against normal leukocytes by the method of Dausset none were found Electrophoretic studies of the serum revealed a normal pattern

The etiology of this syndrome is unknown In some patients urinary hormone studies have revealed cyclic variation in gonadotropin and/or estrogen excretion corresponding to the neutropenic cycles whereas other patients have shown no such pattern In some women the neutropenic cycles have been correlated with the menstrual cycle whereas in others they have not In one of the former groups hysterectomy and bilateral oophorectomy failed to alter neutropenia

The serum of 2 patients with cyclic neutropenia has been injected into normal persons or into guinea pigs without evidence of a neutropenic response Splenectomy performed in 11 patients was followed by improvement of symptoms

(8) J A M A 168 270 272 S pt 20 1958

LEUKOCYTOSIS AND LEUKOPENIA

Fetomaternal Leukocyte Incompatibility was studied by Rose Payne and Mary R Rolfs[7] (Stanford Univ) Isoleukoagglutinins are known to develop primarily in patients after multitransfusions A possibly different kind of agglutinin for white blood cells such as that related to aminopyrine leukopenia has also been described Therapeutic administration of blood and aminopyrine may not be the only stimuli for leukoagglutinin production Two groups of investigators have drawn on the analogy to Rh antibody formation and have considered the possibility that fetal leukocyte antigens might act as stimuli to the mother

Among 144 pregnant multiparous women leukoagglutinins were noted in 25 (17%) The fetus appeared to be the only stimulus for leukoagglutinin formation in 18 (68%) of the 25 as they had never received transfusions or intramuscular injections of blood Isoleukoagglutinins of the maternal serums agglutinated the leukocytes of 10 of 12 of the respective newborn infants and 12 of 13 of the respective spouses thus suggesting the inheritance by the offspring of the leukocyte factor of the father Maternal sensitization to leukocytes appears to develop in a manner analogous to Rh sensitization

The main clinical significance of leukoagglutinins has been their responsibility for many instances of febrile transfusion reaction The demonstration that women may possess leukoagglutinins after fetal stimulation when leukocyte incompatibility exists may explain in part at least why some women have febrile transfusion reactions with a history of no or few transfusions Since these transfusion reactions due to leukoagglutinins can be prevented by administration of blood from which most donor leukocytes have been removed precautions should be taken to prevent this type of febrile transfusion reaction in parous women

It cannot be clearly stated whether or not the leukocyte factors detected by leukoagglutinins from parous women are inherited as simple dominants They were present in 7 families for 2 successive generations and in 1 family for 3

(7) J Cl n I v t 37 1756-1763 Dec mbe 1958

creased eosinophils and basophils or Auer bodies and the leukemic hiatus in the myeloid cells were not observed

These findings may help to distinguish leukemoid reaction from true leukemia The changes are characteristic and definite in the bone marrow It is important to recognize this change and its similarity to leukemia

► [In our experience the peripheral blood is easier to distinguish from leukemia than is the bone marrow Rarely are there sufficient numbers of young myeloid elements to correspond to those of the usual patient with chronic myelogenous leukemia The absence of anemia and of alterations in platelet numbers is also a useful indication in the peripheral blood —E I]

Febrile Transfusion Reactions in Patients with Leukocyte Agglutinins Sven Age Kulmann[1] (Univ of Copenhagen) studied 33 transfusions in 3 patients who had leukocyte agglutinins Following 25 of these transfusions fever (rise in body temperature over 1 C) occurred after 4 other transfusions the rise was 0 5 0 9 C The 1st hour after start of transfusion body temperature remained unaltered During the 2d hour temperature rose gradually reaching maximum after 2¼ 6 hours Maximum temperature was generally of 1 2 hours duration then gradually declined to normal 8 hours or more after start of the transfusion Pulse and respirations correlated with the change in temperature The fever might or might not be preceded by chills but was never accompanied by cough or shortness of breath Pn k pains were present twice but not the typical lumbar pain Vomiting was recorded once Shock was not observed Jaundice did not develop in any patient Plasma hemoglobin concentration did not change and the urine contained neither hemoglobin nor protein

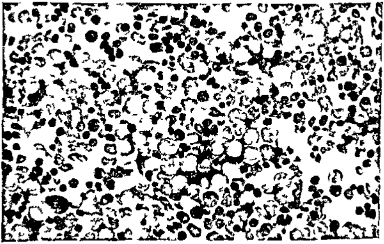
Careful cross matchings including indirect Coombs test always showed perfect red cell compatibility Repeated investigations revealed no irregular red cell antibodies Cell suspensions washed two or three times still elicited reactions

Leukocyte compatibility tests were made in 6 instances and always showed incompatibility between the recipient s plasma and donor s leukocytes All transfusions with demonstrated leukocyte incompatibility caused rise in body temperature No donors could be found who had compatible leukocytes but when blood was separated into two to three fractions by differential sedimentation before being transfused the fraction containing plasma and platelets in suspension

(1) D h M B ll. 5 178 183 J 1958

and neutropenia in some but no complete remissions were observed Therapy in these patients has had little effect on neutropenia

Leukemoid Reaction in Bone Marrow Associated with Malignant Neoplasms The leukemoid reaction is a peripheral leukocytosis with a shift to the left in the granulocytes It occurs with malignant tumors particularly with bone



F g 62 S a f bone m w c llected p t mort m show g hype ll l ty myel d h perpla and ased n mb f pla ma lls N t the ma y yel cyt s W ght G m a t ed d f m × 73 (Co rtesy of Che H P d Walz D V Am J Clin P th 29 34 349 Ap l 1958)

metastases The leukemoid reaction can be distinguished from leukemia only by study of the bone marrow

Hammond P Chen and Donald V Walz[9] (State Univ of Iowa) studied 24 patients with malignant tumors predominantly carcinomas primary in the lung pancreas stomach bladder and rectum Each had definite leukocytosis with counts as high as 30 000 The bone marrow showed a definite pattern hyperplasia of the early myeloid elements with conspicuous increase in myelocytes and erythroid elements decreased but not absent (Fig 62) The myeloid hyperplasia was confined to the myelocytic stage without any proportionate increase in blasts or promyelocytic forms and without any arrest of maturation at any developmental stage The usual findings in chronic myeloid leukemia such as in

(9) Am J Clin Path 29 345 349 Ap 1 1958

for implantation Immediately after sacrifice the entire bone marrow was taken from both femora minced and fixed then implanted into the blastoceles of young gastrulas of Triturus vulgaris The embryos were reared for 10 14 days in sterile solution fixed embedded in paraffin and serially sectioned

Of 66 successful takes after implantation of normal bone marrow from 5 rats 98% showed mesodermal growth im petus No cephalic structures or sensory organs were encoun tered but one third had a short spinal cord primordium at the tip of the induced tail (Fig 63) Some larvae showed dis



Fg 63—A mal t eated w th ormal bon marrow Secondary tail de loped in ent al p d rm I t ri port on f secondary ta l is primo d um f add t on l l mb (Co rtesy f T omen S d S én L. J N t Ca c I st. 19 1095 1105 Dec mbe 1957)

persed neural cells or aggregations of cells The rest of the induced structures were mesodermal most commonly a secondary pronephros The bone marrow of 4 leukemic rats was practically devoid of inductive action The bone marrow of the fifth rat in which the peripheral blood picture was more benign differed from that of the others and yielded a definite reaction in half the experiments No evidence of an inhibitory substance was found because when normal and leukemic tissues were simultaneously implanted the result was the same as in the experiments with normal bone mar row alone

The authors conclude that in leukemic bone marrow one or more agents are lacking or inactivated that are always present in normal bone marrow and that after implantation into a young gastrula bring about formation of additional mesodermal structures from the ectoderm Interpretation of

was well tolerated whereas that containing the red and white cells elicited the usual transfusion reactions The reactions cannot be accounted for by pyrogens bacterial contamination plasma intolerance platelet incompatibility or red cell incompatibility Reactions were elicited only when a certain minimum of leukocytes was transfused

Febrile reactions were caused by reaction between the leukocyte agglutinin of the recipient s plasma and the leukocytes transfused The reasonable way to avoid these reactions would be to select donors with compatible leukocytes This is difficult because many such patients have serum that is nearly panagglutinating It seems easier and safe to transfuse these patients as did Brittingham and Dousset with otherwise compatible blood that has been rendered poor in leukocytes

► [The classic observations of Bennett and Beeson in rabbits and of Cranston *et al* in man concerning the nature of bacterial pyrogens showed that leukocyte injury was invariably involved in such reactions The only animal tissue that in the absence of a bacterial pyrogen was a source of a fever producing material in animals was the leukocyte Such observations in man confirm that conclusion —Ed]

LEUKEMIAS AND RELATED DISORDERS

Embryonic Inductive Action of Normal and Leukemic Bone Marrow of the Rat Certain parts of the embryo possess the capacity to regulate differentiation of other parts Adult tissues too are capable of induction and apparently contain certain active factors The inductive action of adult tissues is not random If tissue growth and differentiation are always regulated by specific factors growth in malignancies should differ markedly from that in the normal and the difference should be detectable with embryonic totipotent undifferentiated tissue

Sulo Toivonen and Lauri Saxen[2] (Univ of Helsinki) injected 0 1 cc of a homogenate prepared from leukemic tumor tissue diluted with saline into rats subcutaneously Leukemia had been induced by gastric instillation of methylcholanthrene which resulted in typical transplantable myeloid leukemia (Shay) After transplantation the rats were killed when leukemia had developed and their tissues were used

(2) J Nat C r Inst 19 1095 1105 December 1957

activated the leukemic agent may in some instances be separated from cells by filtration and transmitted by inoculation into newborn mice of susceptible strain as recently observed by Kaplan

Psychologic Factors and Reticuloendothelial Disease IV Observations on Group of Children and Adolescents with Leukemia Interpretation of Disease Development in Terms of Mother Child Unit William A Greene Jr and Gerald Miller[4] (Univ of Rochester) interviewed one or both parents of 33 children with leukemia or lymphoma at the time of the diagnostic work up and during the course of the illness A few histories were also obtained from the patients

The main symptoms and signs noted by the parents before apparent onset of the disease were anorexia apathy leg or joint pain fatigue irritability fever purpura or bleeding pallor weakness lymphadenopathy anxiety weight loss enuresis sadness or weeping refusal to walk breath holding and vomiting The most common were anorexia and apathy

The advent of a sibling rival displacing the patient in relation to the mother occurred in 17 cases 12 involving an actual sibling or a current pregnancy Change of home occurred in 19 instances Beginning school (nursery kindergarten or primary) or changing school was a separating event in 13 cases

The interviews revealed that the mothers had been depressed for weeks or months before diagnosis of disease in the patients Frequently the emotional distress in the mother was related by her to the same events already described as losses and separations for the patient In several instances it was related to her separation from the child who was going to school

Seventeen patients had had frequent relatively severe infections involving mainly the upper respiratory tract colds tonsillitis otitis pneumonia of varying severity and exanthemas Four of this group had had moderately severe bronchial asthma 1 had had severe asthma for 9 years and a number were said by the parents to have almost died at some time of pneumonia or meningitis Eight patients had shown fewer infectious processes but had been considered to

(4) P y h m M d 0 1 4 144 M Ap 1958

these studies may be that the factor regulating normal leukopoiesis is destroyed or absent in myeloid leukemia and that differentiation is consequently disturbed

Attempt to Recover Filtrable Agent from X ray Induced Leukemia It is difficult to interpret experiments dealing with cell free transmission of mouse leukemia One obstacle is that leukemia can be induced in mice not only by inoculation of filtrates containing a transmissible oncogenic agent presumably a virus but also by other apparently not specific means such as application of certain carcinogenic chemicals injection of estrogenic hormones or total body x irradiation Theoretically these nonspecific means may have their effect indirectly by activating latent viruses carried in inactive form by apparently healthy hosts

To test this hypothesis Ludwik Gross[3] (VA Hosp Bronx N Y) induced leukemia in low leukemia strains of C_3H or C_{57} Brown mice by total body x irradiation then inoculated filtrates from the radiation induced lymphomas into newborn C_3H mice Thymic lymphosarcomas or generalized leukemia developed in 56 (48%) of 116 irradiated mice but not in 93 untreated litter mate controls Incidence of *spontaneous leukemia could be considerably reduced by* thymectomy Similarly thymectomy rendered mice resistant to radiation induced lymphomas

Leukemic thymic and mesenteric tumors and livers and *spleens from the C_3H or C_{57} Brown donors with thymic* lymphosarcomas or generalized leukemia were used to prepare centrifuged or filtered extracts The integrity of the filter was proved by Escherichia coli blocking The extracts were inoculated into newborn C_3H mice less than 16 hours old Of 148 mice inoculated 16 (11%) developed leukemia and 7 (5%) parotid tumors In contrast of 186 mice inoculated with cell free filtrates from normal mice organs only 1 (0 5%) developed leukemia whereas 14 (7 5%) developed parotid tumors Incidence of leukemia in this control group did not exceed that observed to develop spontaneously in untreated C_3H mice

The results suggest that mice of low leukemic strain such as C_3H or C_{57} Brown may carry a latent leukemic agent of low pathogenic potential Triggered by ionizing radiation such an agent may induce leukemia in its carrier host Once

(3) Acta haem t 19 353 361 J 1958

Formation of Myeloma Protein by Mouse Plasma Cell Tumor A homogeneous plasma globulin in high concentration frequently accompanies multiple myeloma but whether the myeloma protein is produced by the tumor cells or is a response of other tissues to the effect of the tumor has not been known A mouse plasma cell tumor associated with a high concentration of homogeneous gamma globulin and other pathologic changes similar to multiple myeloma in man has been discovered Daniel Nathans John L Fahey and Michael Potter[5] (Nat l Inst of Health) administered a labeled amino acid to mice bearing such a tumor then determined the radioactivity of the myeloma protein in the tumor and in the plasma

The tumor and plasma myeloma proteins prepared by column chromatography were homogeneous and had identical properties Both were homogeneous by paper electrophoresis and had the same electrophoretic mobility Ultracentrifuge analyses indicated a homogeneous protein in both instances with essentially identical S 20 values 6 4 for the plasma protein and 6 6 for the tumor protein

Time curves for the specific activities of tumor and plasma myeloma proteins after intravenous C^{14} lysine injection showed marked differences indicating clearly that the two proteins were in different pools The specific activity of the tumor myeloma protein (precursor) exceeded that of the plasma myeloma protein (product) in the early part of the curve was equal to the specific activity of the plasma protein at the point of maximum of the latter and was less than the specific activity of the plasma protein beyond this These results indicated that myeloma protein is synthesized in the tumor

► [It i well to have this probability clearly made a certainty —Ed]

Review of 51 Cases of Multiple Myeloma Emphasis on Pneumonia and Other Infections as Complications Harry Glenchur Horace H Zinneman and Wendell H Hall[6] (Univ of Minnesota) established diagnosis in the 51 patients by biopsy of bone marrow accessible tumor or autopsy and by serum protein electrophoresis Of the 51 patients 28 (55%) had one or more episodes of pneumonia exclusive of terminal pneumonias during the course of their disease A total of

(5) J E p M d 109 121 130 J l 1958
(6) A M A A h I M d 103 173 184 F b ry 1959

have feeding problems since birth and the other 8 had been unusually healthy active and gregarious without any of the usual contagious diseases and not even colds

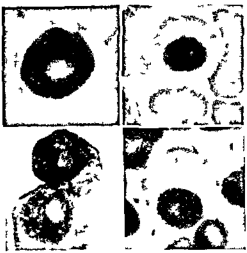
Age range of the mothers was 25 53 and religious affiliations were Catholic 19 Protestant 12 and Jewish 2 Generally they had no serious physical disease currently or in the past Most were consciously preoccupied with ideals of being model mothers well beyond their physical and psychologic capabilities In most mother child relations the mother had assigned a role to the child entirely disproportionate to age Many children irrespective of age were considered babies others as little mother or little man In a number of cases the child was viewed as the patient's mother herself The fathers ages ranged from 25 to 56 years In many families the father was the subordinate parent and was particularly anxious or passive in his role outside the family

The findings suggest that in children as well as in adults separation with depression may be one of the conditions determining the manifest development of leukemia Factors contributing to the childhood peak in leukemia incidence between ages 2 and 5 include the biologic determinant that this is the period in the life of a first born child when the first sibling or two arrive Further this is the period when attempts are being made to resolve the oedipal conflicts and when school is being started

The patients in this study were unselected No control group of children was studied since a suitable group could not be determined Each patient was assumed to serve as his own control

► [Any serious suggestion as to the cause or cure of acute leukemia deserves attention Do these observations offer such a hope? This is the fourth time since 1954 that the senior author and his associates have made the suggestion in print that emotional factors may predispose to leukemia first in children and now in adults This is not beyond possibility Aside from some entirely novel mechanism the emotional stress itself might induce significant changes in habits of diet sleep or resistance to infection, endocrine activity use of drugs etc What is the evidence? So far the absence of any reported effort to analyze a comparable or control series permits no yes or no answer A bland apology is offered for the lack of such controls rather than any account of repeated efforts to find or examine such a series This is not as it should be because the work of the authors offers nothing secure on which others might build and its methodologic defects are no credit to the important field of psychosomatic research in which other workers do find it possible to proceed according to acceptable scientific standards —Ed]

plasmacytic response is usually normally cellular and the plasma cells mainly mature uniformly distributed often related to reticulum cells and rarely more numerous than 20% of the total count In myelomatosis the marrow is most often hypocellular and the plasma cells mainly abnormal shifted to the left focal in distribution rarely associated with retic



Fg 64 (l ft) —Typ l my l m plasma ll F lgen Jen d d f om ×800
Fg 65 (right) —Imm t pla m ell n c s f pl m yt p Feulg n J d d f m ×800
(C rtesy f Ab rn W A J Cl n P th 11 3 6 329 J ly 1958)

ulum cells and usually more numerous than 20% of the total count These criteria are true of large groups but cannot be applied accurately to individual cases

The nucleolus of the myeloma cell is always abnormal and often strikingly hyperplastic W A Aherne[7] (Radcliffe Infirm Oxford England) proposes that assessment of the nucleolus nucleus (n N) ratio is a reliable means for morphologic distinction between plasmacytic responses and myelomatosis The average n N ratio calculated from the ratios of 25 random cells in each of 10 cases of plasmacytic response ranged from 0 29 to 0 22 (mean 0 26) In 10 cases of myelomatosis it ranged from 0 49 to 0 32 (mean 0 41) The boundary between the two categories is 0 31 and there is no overlap

(7) J Cl P th 11 3 6 329 J ly 1958

76 episodes occurred averaging 2 7 bouts/patient Results of therapy were good except in 2 patients who had slow resolution In 2 patients prophylaxis with sulfadiazine or penicillin orally did not prevent further attacks of pulmonary infections Most of the infections involved the lower lobes more often the right lower lobe Pathogenic bacteria were isolated in only 8 episodes whereas normal inhabitants of the oral respiratory tract were isolated from the others

Electrophoresis of the serum in these 28 patients showed gamma myeloma pattern in 8 nine had high globulin content but the pattern was not determined 7 had no globulin elevation and in 6 gamma globulins were low Only 1 patient with pneumonia had normal serum protein pattern 2 had beta myeloma pattern and 2 others had abnormal M myeloma peak Apparently recurrent pneumonia may occur with all types of myeloma patterns but the common denominator of the protein patterns in patients with myeloma and recurrent pneumonia is decrease of normal (immunologically active) gamma globulin

One third of the patients died with pneumonia Antibiotic therapy though previously effective did not prevent rapid terminal course Bacteremia occurred in 2 patients Cyanosis hypotension and peripheral vascular collapse were common Leukocyte response to pneumonia was significantly lower than normal Of 28 patients who came to autopsy 19 had pleural adhesions indicating previous pulmonary infections Other infections exclusive of pneumonia and bacteremia were present in 29 (57%)

The factors contributory to recurrent pneumonias in multiple myeloma are probably multiple and additive Defective antibody production is probably the most important factor This is similar to agammaglobulinemia In both there is profound reduction of immunologically active serum globulins As in agammaglobulinemia the delayed type of bacterial hypersensitivity is not altered

Repeated bacterial infections especially pneumococcic pneumonia are important often early complications of multiple myeloma Antibiotics are effective unless their use is delayed

Differentiation of Myelomatosis from Other Causes of Bone Marrow Plasmacytosis *is often difficult A number of* broad differences have been distinguished The marrow in

The pattern of B_1 binding protein distribution on anion exchange cellulose chromatography is consistent with a single protein entity characteristically eluted after the major albumin peak and also after a peak containing considerable amounts of alpha$_2$ globulin but before the peaks of alpha$_1$ glycoprotein and ceruloplasmin The association of B_{12} with the alpha$_1$ component is consistent with the findings on electrophoresis of whole serum and suggests that the increased serum B_1 binding capacity in chronic myelocytic leukemia is due to an increased amount of the normal B_1 binding protein The elevated B_{12} level in chronic myelocytic leukemia may be due to abnormal metabolism of the B_1 binding protein It is uncertain whether this is directly related to the myelocytic disorder or is a separate manifestation of the basic disease process

Alkaline Phosphatase of Mature Neutrophils in Chronic Forms of Myeloproliferative Syndrome Considerable evidence indicates an interrelationship between polycythemia vera myeloid metaplasia and chronic granulocytic leukemia as well as with acute granulocytic leukemia and acute erythremic myelosis It is highly probable that the primitive multipotent mesenchymal cell matures in various directions resulting in proliferation of cellular blood elements and fibrous tissue The differences observed would then be caused by (1) the cellular element predominantly involved (2) phase of disease in which the patient is seen and (3) acuteness of the process Chemical and cytochemical methods have been reported to show considerable differences in the amount of alkaline phosphatase in the mature neutrophilic granulocytes of polycythemia vera myeloid metaplasia and chronic granulocytic leukemia

W J Mitus L J Bergna I B Mednicoff and W Dameshek[9] (Boston) studied 15 patients with polycythemia vera 4 with transitional disease 23 with myeloid metaplasia and 16 with chronic granulocytic leukemia Peripheral blood smears were stained for alkaline phosphatase and mature neutrophils were examined and scored Average score in 10 normal patients was 30 ranging from 16 to 53 In polycythemia vera the average score was 205 with a range between 165 and 266 In the transitional disease the scores were 154 206 228 and 235 average of 206 In myeloid meta

(9) Am J Cl P th 30 85 294 O t b 1958

Morphology was of secondary interest but certain features appeared typical of the myeloma cell nucleus The nucleolus was usually central or slightly eccentric and the nucleolar membrane thick (Fig 64) The nucleolar substance occasionally showed a curious bluish refractility Most cells showed prominent chromatin associated with the nucleolus However in the normal immature plasma cells (Fig 65) the nucleolus even when large was always delicately bounded The Feulgen technic which brings out these differences is simpler more delicate and more controllable than the Unna Pappenheim procedure Romanowsky stains are unsuitable as they often obscure nucleoli completely

These results confirm the visual impression of greater nucleolar enlargement in myelomatosis than in other forms of marrow plasmacytosis This difference in size supplemented perhaps by differences in structure may be of practical value in diagnosis

► [Usually of course serum paper electrophoresis will show characteristic sharp peaks in myeloma —Ed]

Identification of Vitamin B_1 Binding Protein in Serum of Normals and of Patients with Chronic Myelocytic Leukemia Virtually all vitamin B_1 in normal serum is bound to serum proteins In chronic myelocytic leukemia serum B_1 may be increased 2 30 times normal Robert S Mendelsohn Donald M Watkin Ann P Horbett and John L Fahey[8] (Nat l Inst of Health) studied the B_1 binding protein of normal serum and of serum from patients with chronic myelocytic leukemia using chromatographic procedures for protein fractionations and microbiologic assays to identify the B_1

The highest concentrations of B_1 in both types of serum appeared in the $alpha_1$ globulins when the proteins were separated by chromatographic columns This was confirmed electrophoretically in the myelocytic leukemia serums but the small amounts present in normal serum precluded electrophoretic separation The protein bound B_1 was eluted in the region just before the site of ceruloplasmin elution from the chromatographic column Qualitatively there was no difference between B_1 distribution in the serum of patients with myelocytic leukemia and in normal serum but as expected the quantitative difference was marked

(8) Blood 13 740 747 Aug 1958

row with simultaneous proliferation of bone marrow elements in various organs especially in the spleen and liver It often occurs late in the course of polycythemia vera Some patients have a history of prolonged exposure to myelotoxic agents usually aromatic solvents but the cause often cannot be determined Histochemical studies of blood cells indicate that there is usually increase of alkaline phosphatase of the mature neutrophils

W J Mitus G J Gherardi I B Mednicoff and W Dameshek[1] (Tufts Univ) examined the surgically removed spleens of 4 patients with myeloid metaplasia Two patients had high alkaline phosphatase levels of the mature granulocytes and 2 had low levels Differences in the splenic pathology in the two types of myeloid metaplasia were in the degree not in kind In patients with low alkaline phosphatase of neutrophils the proliferative lesion was more pronounced and the degree of immaturity of the white cells was more striking In splenic imprints the lymphocytes were considerably decreased and the size and number of lymph follicles in histologic sections were decreased The proportion of primitive granulocytes (blast cells and myelocytes) was much greater than in patients who had high alkaline phosphatase of neutrophils Coarse reticulum fibers were more striking and more diffusely increased

The patients with low alkaline phosphatase of the granulocytes are considered to have more advanced myeloproliferation Morphologically and cytochemically some cases are similar to chronic granulocytic leukemia but because the clinical courses are initially entirely different the similarity in pathology may indicate that these are two different but related processes

► [Or different stages of the same process Let us hope that Dameshek who saved many a spl t hair by the introduction of the dynamic and inclusive term myeloproliferative disorders will not now essay too sharp static dist nctions among them —Ed]

Leukemic Reticuloendotheliosis is considered by Bertha A Bouroncle Bruce K Wiseman and Charles A Doan[2] (Ohio State Univ) to be a definite hematologic and pathologic entity They report 26 cases studied during the past 8 years Diagnosis was confirmed by peripheral and bone marrow studies using supravital and Wright s stains Leukemic

(1) A M A Arch P th 67 188 196 F b ry 1959
(2) Blood 13 609 630 J ly 1958

plasia the patients fell into two distinct groups those with high scores averaging 148 and those with normal scores averaging 8 In chronic granulocytic leukemia the patients had scores of 0 4 average 0 8

Five patients with polycythemia vera showed excellent response to P^{32} in decline in hemoglobin levels to normal but in 4 alkaline phosphatase scores remained unchanged and in 1 remained high Three patients with myeloid metaplasia 2 treated by splenectomy 1 by Myleran® had persistently high alkaline phosphatase scores after treatment Two patients with chronic granulocytic leukemia who originally had low scores continued to have low scores after treatment with Myleran® whereas in another a polycythemic phase developed that was indistinguishable from myeloid metaplasia and this patient died in blast crisis His alkaline phosphatase rose to 59 during the myeloid metaplasia like phase and to 211 terminally

Careful comparison of the two types of myeloid metaplasia as discriminated by the alkaline phosphatase revealed no apparent differences in the cause The peripheral blood of those with normal alkaline phosphatase scores revealed more immaturity of the cells bringing these cases closer to those of chronic granulocytic leukemia This may indicate true malignant transformation and a link between the rather benign proliferations of polycythemia vera and myeloid metaplasia on one side and the distinctly malignant process of chronic granulocytic leukemia on the other The leukemic cells cannot produce the enzyme in response to stimuli or agents that in apparently normal persons cause considerable increase The defect indicates abnormal cellular metabolism and abnormal chemical structure of the cell most likely closely linked to the malignant process itself

In some patients with chronic granulocytic leukemia the mature neutrophils again acquired the ability to produce alkaline phosphatase during complete and sustained remissions This finding tends to indicate good prognosis regarding length of remission Whether it indicates complete reversal of the leukemic process and complete repopulation of bone marrow with normal cells is unknown

Cytochemistry of Myelofibrosis with Myeloid Metaplasia in Relation to Spleen Changes Myelofibrosis with myeloid metaplasia is gradual fibrosis and sclerosis of the bone mar

The spleen weight ranged from 2 500 to 3 800 Gm Bone marrow at autopsy showed pronounced proliferation of the reticulum cells

Morphologic identification of leukemic reticuloendotheliosis is best and most accurately made by study of living cell preparations preferably supravitally stained In most of the



Fig 66—Tw t l m ll W ght t h w g rr g l tl f yt pl m wh h t ky bl N l h m t pp po gy l d f m bo t ×200) (C rt y f B l B A t l Blood 13 609 630 J ly 1958)

patients previous diagnosis had been made elsewhere in hematologic laboratories as acute or chronic lymphatic leukemia

The acute and subacute forms of leukemic reticuloendotheliosis have thus far proved resistant to all known therapy Splenectomy should be reserved for patients with the chronic forms with predominance of splenic involvement and with definite complicating secondary hypersplenism

► [This is an important clinical article Some of these patients often go undiagnosed for some time before the peripheral blood or bone marrow become sufficiently involved to suggest leukemia Histiocytes may sometimes most easily be found in the first drop of blood from the ear lobe We have been impressed with a greater incidence of infiltrative skin lesions than not d here —Ed]

Neurologic Complications of Leukemias and Lymphomas encountered over a 3 year period in 1 264 patients (table) were reviewed by William E Hunt Bertha A Bouroncle and

reticuloendotheliosis is a rare disease with incidence of about 2% of all leukemias The sex ratio among these 26 patients was 21 men to 5 women Age was 30 50 in 12 patients 50-70 in 10 and 4 were over 70 Onset was usually insidious The commonest symptoms were weakness and easy fatigability Four had hemorrhagic diatheses 4 had severe pain in the left upper quadrant and in 1 infiltrative erythematous skin lesions were noted initially None of these symptoms or signs are specific

The commonest physical finding was splenomegaly which was present in 25 patients The size of the spleen fluctuated in the same patient during exacerbations and remissions of the disease Hepatomegaly was noted in 15 lymphadenopathy in only 9 and infiltrative skin lesions in 3 Infection was a common complication occurring in 15 patients

Of the 25 patients available for follow up 9 are living 2 less than 1 year after onset 4 from 1 to 2 years 2 from 2 to 5 years and 1 7 years after onset Of the 16 patients who died 4 lived less than 1 year after onset 6 from 1 to 2 years 4 from 2 to 5 years 1 seven years and 1 lived almost 16 years after onset

Initial observations showed severe anemia most frequently normocytic normochromic and secondary to replacement of normal marrow elements by reticulum cells In 6 patients the anemia was frankly hemolytic Leukopenia was the commonest finding with initial white cell counts of 1 000 5 000 cells/cu mm in 15 patients Absolute and relative neutropenia was present in 17 Marked thrombocytopenia was noted in 12

Bone marrow aspirations were done in all 26 patients In 20 (77%) the sample was aspirated with difficulty and no marrow fragments were obtained The samples were hypocellular and showed 30 94% reticulum cells with scattered myeloid erythroid and lymphoid elements Diagnosis of leukemic reticuloendotheliosis was confirmed by finding in the peripheral blood and bone marrow films the typical cell—the free reticulum cell or histiocyte In fixed film with Wright s stain (Fig 66) the cytoplasm was irregular in outline and sky blue The nuclear membrane was distinct and heavy and the chromatin appeared spongy

Histologic observations in the spleen liver and lymph nodes showed the spleen to be most extensively involved

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Neurologic Complications of Leukemias and Lymphomas encountered over a 3 year period in 1,264 patients (table) were reviewed by William E Hunt Bertha A Bouroncle and

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Histologic observations in the spleen liver and lymph nodes showed the spleen to be most extensively involved

No surgery is recommended for this type of neurologic complication Subtemporal decompression although a rational approach is rarely necessary Chemotherapeutic agents alone do not seem to control the syndrome probably because of the failure of these drugs to cross the blood brain barrier It might be that successful control of the systemic aspects of the disease permits the neurologic infiltration to occur in an area to which the drug does not gain access The authors did not use intrathecal chemotherapeutic agents Hydrocephalus and the more massive infiltration of brain stem cord and roots are rare

In Hodgkin s disease the spinal extradural granuloma and intracerebral mass lesions are best treated by x rays Nitrogen mustard is also effective in control of the extradural granulomas however local x ray is more rapid and lasts longer Both agents can be used with maximal efficacy if the patient s general condition and hematologic picture will tolerate nitrogen mustard

Some bizarre neurologic syndromes obviously intra axial and/or intraneural without autopsy material were observed Some of these may be infections some the result of vascular changes following x ray therapy and some are certainly caused by intra axial infiltration The latter group in the brain stem and cord have been found at operation and at autopsy

► [A number of case reports x rays and photomicrographs illustrate the original —Ed]

Anuria Complicating Treatment of Leukemia Three cases are reported by Robert A Kritzler[4] (Columbia Univ) The cause of the anuria was due wholly or in part to increased excretion of uric acid complicating treatment In 10 such cases reported thus far 8 of the patients were over age 50 Anuria after treatment may occur without prior evidence of impaired renal function Among 7 patients in whom nonprotein nitrogen was determined before treatment it was normal in 5 Of 5 patients in whom the kidneys were examined microscopically 3 showed no leukemic infiltrates

Of the 10 patients 9 had chronic leukemia (6 myeloid 3 lymphatic) In each circulating leukocytes were high before treatment and considerably lower at the onset of anuria The interval between beginning of treatment and beginning

(4) Am J M d 25 53 538 Oct be 1958

John N Meagher[3] (Ohio State Univ) The leukemias frequently invade the leptomeninges and Virchow Robin spaces so as to produce increased intracranial pressure caused by the increased mass of the brain without localized mass lesions hydrocephalus or focal neurologic dysfunction Lymphosarcomas behave similarly

The authors compared this to the syndrome of benign idiopathic intracranial hypertension or hydrops because of the normal air studies in the presence of increased intracranial pressure The symptoms are usually headache lethargy and vomiting Papilledema is prominent and may progress to secondary optic atrophy and blindness Seizures are rare Abducens palsy may develop late but true focal neurologic deficit does not seem to occur The condition may persist for weeks and may recur after effective treatment The EEG usually shows a mild diffuse abnormality Biopsy of the brain is diagnostic but unnecessary Cerebrospinal fluid findings may be diagnostic They consist of an increased pressure and pleocytosis of up to 2 000 cells usually called lymphocytes Supravital studies show these to be leukemic cells Sugar levels do not appear to be regularly reduced by the pleocytosis In doubtful cases the cerebrospinal fluid seems to be the best diagnostic criterion especially with the aid of supravital technics

CLASSIFICATION OF 1,264 PATIENTS WITH LEUKEMIA AND LYMPHOMA SEEN DURING 1954 57

Leukemia				Lymphoma			
Type of Leukemia	No of Patients	Neurologic Complication: Hemorrhage	Neurologic Complication: Leukemic Infiltration	Type of Lymphoma	No of Patients	Neurologic Complication: Hemorrhage	Neurologic Complication: Infiltration
Acute lymphoblastic	145	22	10	Hodgkin	237	3	13
Chronic lymphatic	330	11	0	Lymphosarcoma	87	3	5
Acute myelogenous	48	11	0	Reticulum cell sarcoma	58	0	0
Chronic myelogenous	140	13	2	Lymphocytic lymphoma ([illegible])	37	0	0
Monocytic	152	21	3	Giant follicular lymphoblastoma	14	0	0
Total	815	86	15		440	6	18

One case of acute my[illegible] with meningoencephalitis

(3) J Neurosurg 16 135 151 March 1959

least during the last 2 trimesters In the 1st trimester even though the drugs have been given to a few patients without ill effect the experimental evidence is so overwhelming that such treatment should probably be avoided Most pregnant women with Hodgkin s disease show localized lesions for which radiation is the treatment of choice In exceptional instances of generalized disease in which therapy with the alkylating agents seems mandatory in early pregnancy the dose must be kept to an absolute minimum

Available evidence suggests that the antimetabolites ami nopterin and mercaptopurine are contraindicated in the 1st trimester as far as the fetus is concerned Colchicine and urethan have been used without harm even in the 1st trimes ter but the experience is too limited to permit conclusions The question of dose in relation to stage of gestation can be answered only with accumulation of clinical experience

A similar situation exists for irradiation Although there is abundant experimental evidence for production of em bryonic abnormalities by irradiation during organogene sis clinical experience with radiation therapy in Hodgkin s disease has so far shown no instance of apparent harmful ef fect on the conceptus Nevertheless therapeutic radiation even of distant lesions should be avoided during the 1st tri mester if possible In the 2d and 3d trimesters radiation therapy can probably be used for lesions distant from the uterus without risk of con enital malformations On the other hand possibility of increase in prevalence of leu kemia or other malignancy in children surviving maternal irradiation is a risk that must be accepted in these patients This risk also applies for both radiation and mutagenic drugs to the genetic changes that may become manifest in future generations

Surgical Management of Hodgkin s Disease is reported by Danely P Slaughter Steven G Economou and Harry W Southwick[6] (Chicago) Of 18 patients treated surgically over 5 years previously for localized Hodgkin s disease 11 (60%) were clinically well In each diagnosis had been es tablished by lymph node biopsy before definitive surgery In 17 surgery was done because only 1 lymph node bearing area was involved and there was no evidence of systemic involve ment In 1 patient with both cervical and contiguous axil

(6) A S g 148 705 710 Octob 1958

of oliguria varied from 2 to 3 days in some patients to 63 days in others Mortality from this complication is high Only 2 patients survived Two died despite diuresis Obstruction of the extrarenal urinary tract by urate precipitate was shown clinically or at autopsy in 8 patients Lavage of both ureters by catheterization from below should be tried first if this fails nephrostomy must be performed

Anuria after treatment of leukemia a rare complication may be prevented by forcing fluids when an antileukemic agent is used Forced fluids increase urine volume and dilute the urinary urate and other substances that may contribute to the precipitate Risk of extrarenal blockage by precipitate may also be reduced by cautious use of antileukemic agents when the circulating leukocyte count is high Precipitous drop in circulating leukocytes appears to be contributory in most patients

Management of the anuria requires adequate but carefully limited fluid intake 1 200 1 500 cc /day Sixth molar lactate or bicarbonate is used cautiously for acidosis Routine use of alkali to dissolve crystals in the urinary tract is dangerous and ineffective

Hodgkin s Disease and Pregnancy Case Reports and Discussion of Treatment of Hodgkin s Disease and Leukemia during Pregnancy are presented by Robert B W Smith Thomas W Sheehy and Harvey Rothberg[5] From 1942 to 1957 57 females aged 15 50 were registered at Walter Reed Army Hospital with the diagnosis of Hodgkin s disease Nineteen (33%) bore children in the course of the disease with a total of 22 pregnancies In most patients Hodgkin s disease was present at the time of conception but in 6 it was discovered during pregnancy or within 3 weeks after delivery In none was therapeutic abortion performed Of the children born 21 were sound and healthy follow up revealed no neoplastic disease No clear cut evidence was found for a deleterious effect of pregnancy on patients with Hodgkin s disease Therapeutic abortion is rarely indicated in such patients

Nitrogen mustard (HN2) triethylene melamine and chlorambucil have been successfully used in human pregnancy without apparent harm to the fetus and the alkylating agents in conventional doses can probably be tolerated at

(5) A M A A h I t M d 10 777 789 N mb 1958

tity within the lymphoma group of neoplastic diseases thus not existing as a variant or tran ition phase It may have a temporary localized phase in which it may be eliminated by aggressive local measures Either adequate irradiation or adequate surgery may produce the same end result but sur gery is preferable for long term welfare because of the pro gressive effects of radiation

► [There is certainly something to be said for radical surgery when Hodgkin s disease appears to be confined to the neck Heavy local irra diation may be just as satisfactory in the opinion of others—Ed]

THROMBOCYTOPENIC AND VASCULAR PURPURAS

Platelet Phosphatides Their Separation Identification and Clotting Activity Aaron J Marcus and Theodore H Spaet[7] (Montefiore Hosp New York) subjected crude phos pholipid extracts of human blood platelets to paper and col umn chromatography on silicic acid The components re solved were phosphatidylethanolamine phosphatidylserine lecithin sphingomyelin and inositol phosphatide

Pho phatidylserine obtained by column chromatography could replace platelets in thromboplastin generation and prothrombin consumption tests An unidentified fraction (phosphatidic acid?) showed thromboplastic activity It has been stated that phosphatidic acid is a metabolic breakdown product of other phospholipids such as phosphatidylethanol amine phosphatidylserine and lecithin This may have oc curred spontaneously during column chromatography An other alternative is that this is a true part of the platelet phosphatide complex which was not separated on paper Clotting activity has been found in preparations containing phosphatidic acid

The fraction containing phosphatidylethanolamine was active but phosphatidylserine and inositol phosphatide were present Thus the role of phosphatidylethanolamine could not be clarified Lecithin and sphingomyelin could not be tested separately since they were eluted together This is possibly due to poor separation of these phosphatides at the low temperatures which were used in the studies The com

(7) J Cl I 37 1836 1847 Dec nb 1958

lary disease both areas were dissected in continuity One of the 17 with disease in the right axilla was treated by axillary dissection and postoperative x ray therapy and survived over 5 years without evidence of disease The other 16 all had only cervical involvement evident 3 in the right and 13 in the left side of the neck Long term survival free from



Fig 67—Nodal involvement from neck dissection specimen for Hodgkin disease Black nodes represent full blown Hodgkin pattern verging on sarcoma a few areas White nodes present normal histologic pattern cross hatched nodes represent those with sed ... only dev ... from normal Stippled nodes are those showing pattern de ... early Hodgkin s paragranuloma ... sarcoma (Courtesy of Slaughter D P et al Ann. Surg 148 705 710 October 1958)

disease ranged from 6 to 13 years All but 1 patient was treated by radical neck dissection 5 had no supplementary irradiation

Three long term survivors had anaplastic lesions diagnosed as Hodgkin s sarcoma and 1 of the 3 had received no irradiation Hodgkin s sarcoma and anaplastic sarcoma are generally considered incurable and unsuitable for any but palliative management

Considerable variation was found in the histologic picture of all nodes studied varying from entirely normal nodes to full blown Hodgkin s disease The gamut of changes ranged from normal through slightly increased eosinophils in some an occasional Dorothy Reed cell to complete replacement of node architecture (Fig 67)

Hodgkin s disease may constitute a distinct pathologic en

tity within the lymphoma group of neoplastic diseases thus not existing as a variant or transition phase It may have a temporary localized phase in which it may be eliminated by aggressive local measures Either adequate irradiation or adequate surgery may produce the same end result but sur gery is preferable for long term welfare because of the pro gressive effects of radiation

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(7) J Cl I t 37 1836 1847 Dec mber 1958

bined fractions had only negligible thromboplastic activity

The phosphatides may also act as anticoagulants At high concentrations the thromboplastic potency was low compared with the results achieved when each test substance was appropriately diluted A variety of lipids may have anticoagulant activity and no specific agent can be identified which is uniquely responsible for the anticoagulant activity shown by excessive platelet concentrations A wide series of dilutions must be studied before it is concluded whether any given compound is coagulant or anticoagulant

The phosphatides will not lose clotting activity as they are further purified if precautions are taken to avoid denaturation Comparatively small amounts of purified phosphatidylserine had the same activity as crude phospholipid preparations This was evidenced by the fact that purified phosphatidylserine gave 200 and 40 fold more activity in the prothrombin consumption and thromboplastin generation tests respectively as estimated on the basis of relative phosphorus content

Relation between Platelet Integrity and Sulfhydryl Groups was studied by J L Koppel Lillian V Novak and John H Olwin[8] (Univ of Illinois) Platelets contain a number of factors concerned with different phases of clotting mechanism Since it is known that in formation of thrombin platelets together with their plasma cofactors produce a powerful intrinsic thromboplastin it has been postulated that intravascular coagulation may be initiated once appreciable amounts of certain materials are derived from platelets Whether release of platelet factors requires actual breakdown of platelets or only changes in their membrane permeability characteristics is not known What is known is that retraction of the fibrin gel requires presence of intact platelets whereas antiheparin and antifibrinolytic activities of platelets are enhanced markedly as a result of lysis Further bleeding tendency associated with thrombocytopathy A is related to functional platelet abnormality resulting in increased resistance to disintegration Thus variations in rate of normal platelet breakdown may have important bearing on several aspects of coagulation mechanism

Freshly prepared human platelets were incubated with phenylmercuric hydroxide a mercaptide forming agent

(8) P oc Sx E p B 1 & M d 100 2 7 2 9 F bru

known to inhibit many sulfhydryl dependent enzymes Platelet destruction occurred rapidly although in the presence of sulfhydryl containing substances such as reduced glutathione or cysteine ethyl ester its rate was markedly decreased Similar findings have been reported for sheep and human erythrocytes

An increased rate of platelet breakdown was observed not only with mercaptide forming agents but also with alkylating substances such as iodoacetate and sulfhydryl oxidizing agents such as iodosobenzoate In all cases studied the effects observed were highly sensitive to concentration and could always be decreased in extent by suitable concentrations of sulfhydryl containing substances such as cysteine or reduced glutathione The results seem to point toward a relation between platelet sulfhydryl groups and the maintenance of platelet integrity

N ethylmaleimide which is highly specific in its ability to react with sulfhydryl groups caused a significant breakdown of platelets in concentration of 10^{-4} M It has been reported that the same material in concentration of 5×10^{-4} M does not hemolyze human red cells although other sulfhydryl reagents do An explanation for the difference between these two sets of observations is not immediately apparent although it may be suggested that interstices of the platelet membrane are larger than those of the red cell thereby allowing access of N ethylmaleimide to the critical sulfhydryl groups of the intact platelet

Studies on Platelets XX Further Characterization of Electrophoretic Anomaly in Serum of Patients with Idiopathic Thrombocytopenic Purpura Patients with idiopathic thrombocytopenic purpura have previously been shown to have a significant increase in protein bound glucosamine and hexoses and an accumulation of carbohydrates in the albumin and gamma globulin fractions of serum Mario Stefanini and Elly Moschides[9] (Tufts Univ) with the technical assistance of Joseph Di Masi and Lorraine Cassidy studied 3 patients with acute and 3 with chronic idiopathic thrombocytopenic purpura to clarify these anomalies

Electrophoretic pattern migration using pH 8 6 barbital buffer gave protein and glycoprotein patterns for normal and purpura serums that were qualitatively similar but each of

(9) J Lab & Cl M d 51 842 849 J 1958

the fractions was quantitatively greater in the purpura serums and the carbohydrates were increased in the albumin fraction The albumin from serum of normal persons behaved as a single component when electrophoretically migrated in phthalate buffer and showed no appreciable stainable carbohydrate material The albumin from serum of patients with idiopathic thrombocytopenic purpura under identical conditions separated into two individual components a faster one (albumin 1) representing 24 36% of all protein (70 85% of the total albumin fraction) and a slower one (albumin 2) representing 3 5 11% of all protein

The major difference between normal and purpura serums was in the total amount and distribution of hexoses and glucosamine in the various serum fractions Patients with purpura showed increased protein bound hexoses and a significant rise of glucosamine The albumin fraction of normal serum contained no appreciable amount of hexoses or glucosamine whereas that of purpura serum contained 15 20% of the total amount of protein bound hexoses and about 30% of the total glucosamine This increase appeared linked to the albumin fraction The amount in the globulin fractions was the same as that in normal serum Hexoses and the greatest part of the glucosamine in the albumin fraction migrated with albumin 1

The significance of these findings remains unclear They do not appear in hemophilic serum or serum from patients with secondary thrombocytopenia due to leukemia or bone marrow aplasia They may indicate autoimmunization against platelets

Macroscopic Studies of Platelet Agglutination Nature of Thrombocyte Agglutinating Activity of Plasma K M Brinkhous E C LeRoy W P Cornell R C Brown J L Hazlehurst and G P Vennart[1] (Univ of North Carolina) describe a test to determine the time and degree of agglutination of platelets

PROCEDURE —Plasma or plasma derivative 1 ml is mixed with 0 25 ml cation solution (calcium magnesium or manganese) incubated for 30-40 minutes at 28 C then 0 2 ml aliquot is added to 0 2 ml platelet suspension and a stop watch started The tube is tapped gently and the moment of appearance of platelet clumps determined Two minutes later the clumps are graded macroscopically on a scale of 1-4+ Microscopic examination reveals the 1+ to have about 5

(1) Proc Soc Exper Biol & Med 98 379 383 June 1958

platelets 2+ to have 10 25 3+ to have 30 100 and 4+ to have over 100 Unagglutinated tests are observed at 2 10 and 30 60 min utes before being considered negative

Three components were essential for rapid agglutination platelets bivalent cations and plasma or plasma derivatives The most reproducible results were obtained from platelets prepared with ethylenediamine tetra acetic acid The plate lets in these preparations were uniform biconvex disks when examined in the hanging drop with phase microscopy Wash ing the platelets as many as 10 times did not alter their ag glutinability A final platelet concentration of 2×10 /cu mm or higher gave the best results With lower concentra tions agglutination times were longer and clumps smaller Storage of platelet preparations at 28 C for 20 hours e lu ed their agglutinability but if stored at 2 C as long as 20 hours then warmed to 28 C immediately before use rea tivity was not changed When the platelets were frozen and thawed or heated to 60 C they did not agglutinate Platelet agglutina tion was delayed or absent in presence of calcium but was rapid with magnesium or manganese The fact that calcium caused clotting but magnesium and manganese did not sug gests dissociation of platelet agglutination and coagulation

Prompt agglutination occurred in all plasmas tested re gardless of the anticoagulant used Resin plasma that had been frozen for 3 months still had its original agglutinating power The thrombocyte agglutinating factor was inacti vated by heating at 52 5 55 C It was still present after dialy sis Plasma and serum retained high agglutinating capaci ties until diluted to concentrations below 6-12% Fibrinogen preparations uniformly revealed high agglutinating activ ity although serum with no detectable fibrinogen was equally active Other experiments showed the thrombocyte agglutinating factor to be distinct from fibrinogen This fac tor in plasma is thermolabile and nondialyzable Under op timal conditions it caused gross platelet clumping in 5 15 seconds It is active in the absence of fibrin coagulation cal cium fibrinogen antihemolytic factor prothrombin and related coagulant factors

The results suggest that the thrombocyte agglutinating factor may act independently of the coagulation process

► [This is a careful study of the essent al cond tions for a pl enomenon that may help to improve the reliabil ty of the exi ti g tests for agglutina tion of platelets by the plasma of certain patients with idiopathic thrombocytopenic purpura —Ed.]

Survival of Blood Platelets Labeled with Chromium 51 Knut A Aas and Frank H Gardner (Harvard Med School) devised a workable technic for in vitro labeling of human blood platelets with Cr^{51} and evaluating their survival after transfusion to normal recipients

TECHNIC —Whole blood 500 ml is collected by gravity into poly vinyl chloride plastic bags containing 50 ml of 1 5% disodium ethyl enediamine tetra acetic dihydrate in saline using Arquad coated 15 gauge male hub needles The first 10 ml is diverted through a Y di vision in the tubing thus excluding tissue juice contamination The blood is centrifuged for 15 minutes the platelet rich plasma is trans ferred to another plastic bag containing 15 ml of 2% Triton in saline then centrifuged at 1 000 g The platelets separate as a creamy but ton at the bottom of the bag The supernatant is withdrawn and saved leaving about 10 ml residual plasma with the platelet button The platelets are resuspended and 300 μc sterile Cr^{51} is injected into the bag mixed and incubated for 15 minutes at room tempera ture (20 22 C) Some of the plasma is then added and the mixture prepared for reinfusion

Cr^{51} labeled platelets were transfused into 30 volunteers with normal platelet counts Heterologous or autologous la beled platelets were used without untoward reactions Each volunteer received only one labeled platelet transfusion thus eliminating concern that platelet sensitization would develop and alter the survival period

The life span of these platelets is 9 11 days Manipulation of the blood in plastic bags is the most satisfactory method for preparing sterile platelet concentrates With practice the procedure from phlebotomy to infusion takes less than 2 hours Throughout the technic the platelets are main tained in a plasma medium since washing in physiologic sa line alters their morphology

Preliminary body surface counting with a scintillation probe suggests transient increased radioactivity over the lungs and liver areas probably as a result of temporary se questration in the reticuloendothelial tissues Within the circulation of the recipient the Cr^{51} activity remains low for the first few hours then gradually rises reaching a peak in 24 hours This 24 hour peak does not appear when throm bolytic plasma factors are present such as in idiopathic thrombocytopenic purpura and in platelet immunization from multiple transfusion

The labeled platelet activity appears to decline in a linear

(2) J Cl I t 37 1 57 1 68 S ptembe 1958

fashion suggesting that this method measures the life span of the transfused platelet The ease of preparing labeled platelets will allow more complete interpretation of thrombocytopenic states Therapeutically there is no advantage over direct transfusion of platelet rich whole blood or plasma concentrates Labeled platelets may be prepared with ease from the average donor using the described method without seeking polycythemic donors with thrombocytosis

Immunoreactions Involving Platelets IV Studies on Pathogenesis of Thrombocytopenia in Drug Purpura Using Test Doses of Quinidine in Sensitized Individuals Their Implications in Idiopathic Thrombocytopenic Purpura N Raphael Shulman[3] (Nat l Inst of Health) determined the antibody concentration using complement fixation in 2 patients with quinidine sensitivity Antibody concentration the morning the purpura was first noted was 50 units/ml and rose within 3 weeks to 300 units/ml then declined (Fig 68) Each of three test doses caused a rise in antibody titer

Regulated intravenous doses of quinidine could be given to produce controlled thrombocytopenia without clinical sequelae White counts done at the same time as platelet counts showed no significant variation Symptoms did not develop Capillary fragility tests and bleeding times were normal even when the platelets were at the lowest level The degree of thrombocytopenia and the rate at which it developed depended on the relative plasma concentration of quinidine and antibody

By relating in vivo changes in platelet levels to concurrent in vitro tests for antibody activity the amount of antibody that attaches to platelets when thrombocytopenia develops is considered insufficient to cause complement fixation or platelet agglutination Platelets do not appear to be destroyed directly by reaction with antibody in vivo The minimal amount of antibody that does attach to platelets in vivo appears to increase their susceptibility to the usual mechanisms of sequestration

Megakaryocytes and blood vessels were not affected directly by the antibody that causes quinidine purpura and hemorrhagic manifestations of the disease were consequent to changes in platelets alone

(3) J E pe M d 107 711 729 M y 1 1958

Survival of Blood Platelets Labeled with Chromium 51

Knut A Aas and Frank H Gardner[*] (Harvard Med School) devised a workable technic for in vitro labeling of human blood platelets with Cr^{51} and evaluating their survival after transfusion to normal recipients

TECHNIC —Whole blood 500 ml is collected by gravity into poly vinyl chloride plastic bags containing 50 ml of 1 5% disodium ethyl enediamine tetra acetic dihydrate in saline using Arquad coated 15 gauge male hub needles The first 10 ml is diverted through a Y di vision in the tubing thus excluding tissue juice contamination The blood is centrifuged for 15 minutes the platelet rich plasma is trans ferred to another plastic bag containing 15 ml of 2% Triton in saline then centrifuged at 1 000 g The platelets separate as a creamy but ton at the bottom of the bag The supernatant is withdrawn and saved leaving about 10 ml residual plasma with the platelet button The platelets are resuspended and 300 μc sterile Cr^{51} is injected into the bag mixed and incubated for 15 minutes at room tempera ture (20 22 C) Some of the plasma is then added and the mixture prepared for reinfusion

Cr^{51} labeled platelets were transfused into 30 volunteers with normal platelet counts Heterologous or autologous la beled platelets were used without untoward reactions Each volunteer received only one labeled platelet transfusion thus eliminating concern that platelet sensitization would develop and alter the survival period

The life span of these platelets is 9 11 days Manipulation of the blood in plastic bags is the most satisfactory method for preparing sterile platelet concentrates With practice the procedure from phlebotomy to infusion takes less than 2 hours Throughout the technic the platelets are main tained in a plasma medium since washing in physiologic sa line alters their morphology

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(*) J Clin Invest 37 1257 1268 Sept pub 1958

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(3) J E pe Med 107 711 729 M y 1 1958

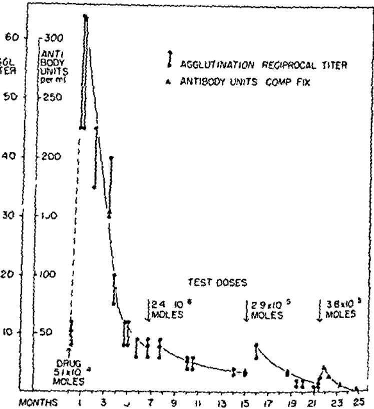


Fig 68 —Ant body conc ntr ti n se um of woman 67 o er 2 yea s n u t pe m ll ter d term ed by omp ment fixat Aggl t n ti n t te sh w range of ec p ocal f s rum d lut > p od ing 1+ plat let agglut t n 1 h ur n tandard gglut n ti n m xtu Drug d e wh h nit t d p r pura was 5 1 10 m l qu n d e su f t (C H O N)₂H SO H O 10 2 × 10 mol qu d n F t t st du ng th m th of bs t 2 4 10-6 mols qu n d n s cond t st d beg nn ng of 16th m nth 1 2 × 1 mol c nch n e + 1 7 × 10 m ls q d e thi d test do 2 d month 3 8 × 10 m l qu id ne (Court y of Shulman N R, J Expr Med 107 711 729 May 1 1958)

If it is assumed that in idiopathic thrombocytopenic purpura an antibody attaches to platelets and leads to thrombocytopenia in a similar manner, its pathogenesis is less puzzling Antigenic stimuli in idiopathic thrombocytopenic purpura could be simple molecules (haptenes) that are ingested formed metabolically or produced by infectious agents in which case the antibody haptene platelet complex might be similar to that in drug purpura In chronic idiopathi hrombocytopenic purpura effective antigenic stimul be

persistent and in the acute disease transient Clinical manifestations could be interpreted solely in terms of factors that affect the sequestration and production rates of platelets by megakaryocytes Beneficial effects following splenectomy would be due to removal of an active site of sequestration and would not affect the underlying basis of the disease If no improvement followed the spleen probably was not the only important site of sequestration

► [These suggested mechanisms of platelet removal are similar to those involved in idiopathic acquired hemolytic anemias and the analogy with red cell sensitization due to Fuadin® is close (Harris J Lab & Clin Med 47 760 1956) —Ed.]

Treatment of Idiopathic Thrombocytopenic Purpura Review of 93 Cases is presented by E J Watson Williams A I S Macpherson and Stanley Davidson[4] (Univ of Edinburgh) Purpura now recognized to be associated with deficient numbers of circulating platelets was first described by Werlhof in 1776 The first definitive treatment was splenectomy reported by Kaznelson in 1916 and this was the only effective therapy for the next 35 years until the introduction of corticotropin and cortisone

Twenty six patients received no treatment other than whole blood transfusions or hematinics Ten of these had long histories of recurrent bleeding into the skin or from mucous membranes seldom severe and gradually subsiding The other 16 had acute onset without warning crops of petechiae in the skin and mucous membranes and bleeding into and from various sites Of 5 who had intracranial hemorrhage 4 died The other 12 who had cases of acute onset underwent apparently spontaneous and permanent recovery The hemorrhage stopped within 14 days of admission and the platelet count began to rise becoming normal within 100 days of onset of symptoms None have had recurrences since and 5 have been followed more than 9 years

These findings suggested the arbitrary division of patients treated with corticotropin corticoids or splenectomy into (1) those in whom onset was less than 100 days before treatment was started and in whom the possibility of spontaneous remission was still present and (2) those with a history of more than 100 days in whom spontaneous remission was unlikely

In 31 patients specific treatment was begun less than 100

(4) Lancet 2 221 226 Aug 2 1958

days from onset of symptoms—in 11 of these within 10 days Among the 11 5 had complete remission which persisted after treatment was stopped One had temporary improvement followed by relapse when the drug was withdrawn and then had a spontaneous remission 30 days later Two patients did not improve while receiving corticotropin but 20 days after treatment was stopped they had spontaneous remissions Three obtained no benefit from steroids and later had splenectomy Among the others 1 was given corticotropin 30 mg daily for 17 days and 13 days later had complete remission Seven received cortisone or prednisolone for 3

RESULT AT INTERVALS AFTER SPLENECTOMY

Period of observation (yr)	Short history cases					Long history cases				
	No	Traced	Well	Presumed well	% Success	No	Traced	Well	Presumed well	% Success
1	17	17	14	—	83	30	29	17	2	65
4	10	10	6	2	80	20	18	8	3	61
8	8	8	5	1	75	14	14	5	2	50
12	4	4	2	1	75	6	6	1	1	33
20	1	—	1	—	—	4	4	1	1	50

weeks or more 3 of these had complete remission starting at the end of the course and 4 did not benefit and had splenectomy Response to steroids was not related to dosage or duration of therapy

In 36 patients therapy was started more than 100 days after onset of symptoms Corticotropin cortisone or prednisolone was given to 23 In 3 this was the only treatment the other 20 also had splenectomy Steroids were given to 11 patients only before operation to 6 only after splenectomy had failed and to 3 both before and after operation

Splenectomy was performed on 33 patients with long histories of purpura—as the only specific treatment in 19 and after 1 administration of steroids in 14 A year after splenectomy 19 of 29 patients (65%) were symptom free and had platelet counts and bleeding times within normal range At 4 years this was true of only 61% and 8 20 years after operation the proportion of those completely relieved was 50% or less (table)

Almost half the patients with short histories of purpura had complete remission during treatment with steroids and maintained the remission after treatment was stopped

About half of those with longer histories improved but this was not maintained for more than 60 days Permanent remission after steroid therapy was common among patients with short histories of purpura but exceptional among those with long histories Apparently permanent remissions are not directly related to the steroids but may in some instances be hastened by treatment Steroid therapy in these cases probably does no more than facilitate their natural tendency to spontaneous remission

Once the acute hemorrhage has passed splenectomy is beneficial Symptoms are immediately relieved bleeding time is shortened and the platelet count rises Improvement persisted in at least 75% of patients followed more than 12 years

Initial management of the patient with a short history of purpura should include blood transfusion to replace any serious blood loss and administration of cortisone (75 mg every 6 hours) or prednisolone (15 mg every 6 hours) for 3 weeks If the platelet count rises during this time it will likely be maintained If no improvement is noted within 3 weeks splenectomy should be performed A good result can be expected in 75% of patients so treated

Patients with long histories of relapsing purpura should also be given a 3 week course of steroid therapy All should have splenectomy during the induced remission or as soon as it is apparent that the treatment has not influenced the platelet count Chances of permanent remission are less than in the *short history group* but 50% *have maintained improvement* 20 years later

► [This survey of therapeutic results in a considerable group of patients in the era of use of both steroids and splenectomy is a valuable contribution —Ed]

Hereditary Capillary Purpura (Willebrand s Disease) The common forms of hereditary hemorrhagic disease are hemophilia including Christmas disease hereditary capillary purpura and hereditary capillary telangiectasia Hereditary capillary purpura accounts for about one fourth of all cases of hereditary hemorrhagic disease A R Horler and L J Witts[5] (Radcliffe Infirm Oxford England) review their experiences with 20 patients with hereditary capillary purpura seen during 1937 54

The condition which affects both sexes with a *slight pre*

(5) Q rt J M d 27 173 185 Ap 1 1958

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(5) Q rt J M d 27 173 185 Ap l 1958

ponderance in females is usually recognized early in life Inheritance of the disease is generally accepted as a mendelian dominant but the pattern is not constant

The hemorrhagic symptoms are bleeding on trivial injury or spontaneous bleeding from the nose gums skin genitals or gastrointestinal or urinary tracts Platelet counts are normal as is platelet morphology but bleeding time is greatly prolonged and the tourniquet test may be positive Coagulation time and clot retraction are normal Normally hemorrhage is arrested in two stages occlusion of the injured capillary by its own contraction aided by agglutination of platelets at the site of injury and blood coagulation The defect in Willebrand s disease occurs in the first stage Microscopic examination of nail bed capillaries shows them to be irregular tortuous and inadequate in contraction after injury These abnormalities result in a prolonged bleeding time

The type of bleeding is different from that in hemophilia although hemarthroses have been reported It is not actually purpuric because petechiae are rare but the tendency to superficial bruising and bleeding from the mucous membranes resembles true purpura Hemorrhage may be severe after one operation and in no way excessive after another The hemorrhagic tendency lessens with age

Treatment is prophylactic avoiding trauma and surgery unless sufficiently urgent to warrant the risk Dental extraction should be carried out in the hospital Transfusion replaces blood loss and counteracts shock There is no coagulation defect in uncomplicated cases so no missing factor must be restored Local pressure may produce ischemia and allow the blood to coagulate Splenectomy is of no value and carries additional risk The value of steroid therapy is not established

One girl aged 20 also had no antihemophilic globulin by the thromboplastin generation test in addition to hereditary capillary purpura A recent study of patients from Aaland where von Willebrand originally investigated hereditary capillary purpura showed 15 to have decreased antihemophilic globulin Probably antihemophilic globulin is more universally decreased in Willebrand s disease than had been realized

► [See also another article on this topic in the next section Coagulation Defects —Ed.]

COAGULATION DEFECTS

Nomenclature of Blood Clotting Factors Acceptance by International Committee on Nomenclature of Four Factors Their Characteristics and International Number is discussed by Irving S Wright[6] (New York Hosp) The first four factors—factor I fibrinogen factor II prothrombin factor III thromboplastin (tissue) and factor IV calcium—are widely known Four further factors have been recognized

Factor V—Synonyms are proaccelerin labile factor plasma Ac globulin thrombogene proprothrombinase prothrombokinase PPCF (plasmin prothombins conversion factor) component A of prothrombin prothrombin accelerator and co factor of thromboplastin Deficiency of this factor results in a hemorrhagic diathesis which is probably inherited and has been described as parahemophilia or hypo accelerinemia This factor *seems necessary for formation* of the prothrombin converting sub tance in the blood and tissue extracts

Factor VII—Synonyms are proconvertin SPCA (serum prothombin conversion accelerator) stabile factor co factor V serozyn kappa factor prothrombinogen co thromboplastin serum accelerator prothrombin conversion factor and prothrombin converting factor Factor VII plays a part in the production of at least three groups of abnormal states (1) A congenital deficiency may produce hemorrhagic phenomena with purpura and bleeding from the mucous membranes (2) Acquired deficiency may occur in liver disease in vitamin K deficiency in the immediate neonatal period and after the administration of prothrombinopenic agents such as the coumarin derivates used in anticoagulant therapy (3) Excesses of factor VII have been found in certain states associated with a high incidence of thromboembolism such as the 3d trimester of pregnancy The level of this substance in the blood is specific Factor VII accelerates the conversion of prothrombin to thrombin in the presence of tissue thromboplastin factor V and Ca^{++}

Factor VIII—Synonyms are antihemophilic globulin antihemophilic globulin A AHF (antihemophilic factor)

(6) Ca d. M A J 80 659 662 Ap 15 1959

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The present study clearly demonstrates that a combination of phosphatidyl serine and lecithin results *in* formation of an active thromboplastic substance In certain tubes the phosphatidyl serine fraction *also* contains minute traces of *inositol phosphatide and an unidentified phospholipid* That the recalcification time and prothrombin conversion factor generation test were the same whether or not these minute contaminants were present indicates that they could not be the thromboplastin factors Also sphingomyelin which may have been a contaminant of the lecithin preparations did not contribute to generation of the prothrombin conversion factor

It is thus relatively certain that the two entities responsible for the thromboplastic activity as measured in these experiments are lecithin and phosphatidyl serine No augmented thromboplastic activity could be generated when the same components were emulsified in water without having been mixed together previously in chloroform solution Neither phosphatidyl serine nor lecithin alone possesses any appreciable thromboplastic activity but when they are dissolved together in chloroform a potent thromboplastic substance results

► [The reader should compare these findings with those of the first article under Thrombocytopenic and Vascular Purpuras —Ed]

Role of Hageman Factor in Initiation of Clotting by Glass Evidence That Glass Frees Hageman Factor from Inhibition is presented by Oscar D Ratnoff and Jerold M Rosenblum[8] (Western Reserve Univ) The factors maintaining the fluidity of blood within blood vessels are unknown When blood is shed and placed in tubes lined with paraffin or silicone it clots lowly but when the same blood is put into glass tubes coagulation is rapid The experiments showed that the clot promoting effect of glass requires the presence of a specific clotting factor This specific substance is absent from the plasma of patients with Hageman trait and of ducks

Hageman trait is a familial disorder in which the clotting time of venous blood is greatly prolonged Nonetheless patients with this syndrome do not show a bleeding tendency Their plasma lacks a clotting factor which can be separated from all others described This substance Hageman factor is essential for the initial stages of clotting in glass tubes

(8) Am J Med 25 160 168 Aug t 1958

PTF (plasma thromboplastic factor) plasma thromboplastic factor A TPC (thromboplastic plasma component) facteur antihemophilique A thromboplastinogen prothrombokinase platelet co factor plasmokinin and thrombokatilysin Factor VIII deficiency represents the classic hemophilia A

Factor IX—Synonyms are Christmas factor PTC (plasma thromboplastic component) antihemophilic globulin B plasma thromboplastic factor B plasma factor X and facteur antihemophilique B Factor IX deficiency produces hemophilia B or Christmas disease This is usually a severe hemorrhagic disorder resembling hemophilia A and inherited in the same way Factor IX like factor VIII is essential for the formation of intrinsic blood thromboplastin It probably enters into the reactions leading to the formation of this thromboplastin forming with CA++ and factor VIII an intermediate product which then reacts with platelet factors III and V

► [Whether or not the coagulationists will enjoy this conversion of private worlds to international living the rest of us will benefit So to quote the original The world grows smaller and nations more fully accept the necessity of living and working together Perhaps this will help to tip the balance in favor of extension of the metric system—Ed.]

Purification and Identification of Brain Phospholipids Associated with Thromboplastic Activity was accomplished by Donald Therriault Thomas Nichols and H Jensen[7] (US Army Med Res Lab Fort Knox Ky) Previous work on isolation of the active thromboplastic phospholipids from brain tissue has shown that the specific activity of the purified fractions never exceeds the specific activity of the original preparation but actually seems to diminish on refractionation

Fractions containing respectively primarily phosphatidyl serine and phosphatidyl ethanolamine were prepared from beef brain tissue according to the procedure of Folch An ethanol extract from acetone dried beef brain tissue was used for the preparation of lecithin by the method of Pangborn Both the lecithin and phosphatidyl serine preparations were further purified by countercurrent distribution in a Craig 100 cell countercurrent distribution apparatus The solvent system consisted of carbon tetrachloride methanol and water in the ratio of 62 35 4

(7) J B I Chem 33 1061 1065 N emb r 1958

part to use of terms based on a particular investigator s in terpretation of his experimental data or the theory of coag ulation in vogue Terms that have functional connotation e g serum prothrombin conversion accelerator should be avoided at least until the exact mode of action of these fac tors is clearly established [See first article in this section —Ed]

The primary hemorrhagic diatheses fall into three groups congenital and acquired hemophilioid states vascular pur puras and thrombocytogenic purpuras Clinical history and physical examination are important Congenital bleeding tendency will be suggested by history beginning early in life of unusual persistent or recurrent hemorrhage after minor trauma Congenital diathesis is unlikely in any patient who has had major surgery without excessive bleeding A sex linked history of a defect transmitted by females and lim ited to males suggests hemophilia or Christmas disease (plasma thromboplastin component deficiency) Hemar throses are present in severe disease of the hemophilioid group but rarely in the purpuras Petechiae and/or mul tiple superficial ecchymoses are usual in purpuras but ex ceeding rare in the hemophilioid states

By three simple screening procedures—platelet count routine bleeding and clotting time—the more severe bleed ing disorders can be readily classified This is not true of milder hemophilioid states or milder purpuras Congenital hemophilioid disorders may be further delineated by one stage prothrombin time and thromboplastin generation tests One stage prothrombin time is normal in hemophilia (antihemophilic factor deficiency) plasma thromboplastin component deficiency Hageman factor deficiency plasma thromboplastin antecedent deficiency circulating anticoag ulant and in platelet factor 3 deficiency but is prolonged in Stuart factor deficiency and in deficiencies of factors V and VII prothrombin and fibrinogen The deficient fraction in the thromboplastin generation te t is the adsorbed plasma in hemophilia the serum in plasma thromboplastin compo nent deficiency adsorbed plasma and serum in Hageman factor deficiency plasma thromboplastin antecedent defi ciency and circulating anticoagulant it is deficient in plate lets in platelet factor 3 deficiency in serum of Stuart factor deficiency and in adsorbed plasma of factor V deficiency

Why patients lacking Hageman factor do not have any bleeding tendency has not been explained

The mechanism by which glass exerts its clot promoting effect was studied in experiments in which normal plasma and plasma deficient in Hageman factor were mixed before treatment with crushed Pyrex glass particles These experiments demonstrated that human or duck plasma deficient in Hageman factor impeded the clot promoting effect of glass on normal plasma but Hageman deficient plasma did not appreciably oppose the clot promoting properties of normal plasma which had already been treated with glass The same results were obtained when barium carbonate was used to promote clotting instead of glass

The authors suggest the following tentative hypothesis In normal plasma Hageman factor is present in an inactive state The inactive state probably results from presence of one or more inhibitors directed against Hageman factor Fluidity of blood within blood vessels is maintained by these inhibitors Exposure of blood to glass or to such other adsorbents as charcoal kaolin or barium carbonate converts Hageman factor to an active form initiating clotting Presumably these adsorbents free Hageman factor from inhibition Once Hageman factor has become active it is rapidly destroyed by an enzyme a mechanism which may protect against its continued action Similar events may lead to formation of intravascular thrombi Perhaps under some circumstances the initiating event in thrombosis is a change in the vascular endothelium so that its surface takes on certain properties of glass Such changes have been described in the endothelium of dying rabbits The endothelial surface thus damaged would serve as a focus at which the changes leading to intravascular clotting would begin

Plasma then may contain two inhibitory mechanisms related to the initiation of clotting the one preventing activation of Hageman factor and the other destroying Hageman factor which has become activated

Hemophilioid States Practical Application of Present Day Concepts of Blood Coagulation to Diagnosis and Treatment are reviewed by Cecil Hougie and Henry M Glover[9] (Univ of Virginia) Recent progress has been clouded by multiple and chaotic nomenclature of clotting factors due in

(9) A M A Arch Int Med 103 239 252 February 1959

canted and tored at +4 C for 30 days Plasma so treated retained normal activities of plasma thromboplastin component plasma thromboplastin antecedent Hageman factor prothrombin proconvertin (factor VII or s rum prothrombin conversion accelerator) Stuart factor and fibrinogen however antihemophilic globulin and proaccelerin fell to undetectable levels The plasma was stored at −20 C in mall aliquots until needed Optimal quantities of Asolectin and barium sulfate adsorbed oxalated bovine serum were added to the plasma immediately before the test as sources of platelet prothomboplastic factor like activity and of accelerin respectively The buffer for all dilutions was Veronal* acetate pH 7 3

In a series of 12×75 mm tubes were placed 0 1 ml aged Na EDTA plasma 0 1 ml Asolectin (0 005%) 0 05 ml barium sulfate ad orbed bovine serum diluted 1 80 and 0 05 ml of either normal or unknown plasmas in serial dilutions The coagulation times for these mixtures after recalcification with 0 1 ml 1/70M CaCl were recorded and the values for tubes containing the unknown plasma were compared with those for tubes containing serial dilutions of normal plasma The average recalcification time for such a system when buffer is substituted for the unknown plasma is 14 minutes the time is hortened to 5 minutes or less (normal 4 ½ minutes) when any one of the following is added instead platelet poor normal plasma plasma from a patient receiving Dicumarol* Seitz filtered normal plasma barium sulfate ad orbed normal plasma and plasmas from patients congenitally deficient in plasma thromboplastin antecedent (1 patient) Hageman factor (1 patient) plasma thromboplastin component (3 patients) proconvertin (1 patient) and proaccelerin (1 patient) However with plasma from none of 6 patients with classic hemophilia diagnosed by the method of Soulier and Larrieu was the prolonged recalcification time corrected to normal in the system described

Thus it appears the diagnosis of classic hemophilia can be made with this artificial reagent which would have the advantage of simplicity and availability of material

Coagulation Defect in Congenital PTA Deficiency Rosenthal and co workers have reported 3 patients with a hemophilia like clotting defect which could not be explained by lack of factors VIII or IX Matching studies with the blood of these 3 patients and hemophilia A and hemophilia B blood led to normalization of the former clotting defects The serum of each patient showed a high concentration of prothrombin Based on these observations Rosenthal ha postulated the existence of a new clotting factor PTA (plasma thromboplastin antecedent)

F Bachmann F Duckert U Fisch F Streuli D Gerber and F Koller (Univ of Zurich) observed 2 women aged 28

( ) S hw z m d W h sch 88 1037 1044 O t 18 1958

Absolute diagnosis of hemophilioid state depends on cross matching the patient s plasma or serum with that of a patient with proved congenital deficiency of the factor under test Provisional diagnosis by routine procedures will usually be correct

In severe unremittent hemorrhage transfusions of fresh or stored whole blood are necessary In hemophilia the levels of antihemophilic factor range from 0% in severe cases to 30% in milder ones To increase antihemophilic activity by 1% about 1 ml fresh normal plasma/kg must be given Usually at least 1 500 ml whole blood or its plasma equivalent less than 24 hours old is required over 24 hours to effect hemostasis in mild cases Severe cases are difficult At least 1 L whole blood is usually required given over as short a period as possible followed by slow maintenance drip infusions Plasma thromboplastin component is more stable in routinely stored bank blood than antihemophilic factor and hemostasis is more easily achieved with transfusions Probably 1 L plasma within 24 hours will suffice in even the most severe cases

► [This is a systematic practical and well illustrated review of the accepted diagnostic and therapeutic aspects of conditions associated with coagulation defects Useful tables and references are included —Ed]

Artificial Reagent for Diagnosis of Classic Hemophilia is described by P Didisheim[1] (Centre Nat l de Transfusion Sanguine Paris) Present methods for the laboratory diagnosis of classic hemophilia (hemophilia A or antihemophilic globulin (deficiency) are (1) modifications of the thromboplastin generation test or (2) tests dependent on the use of plasma from a patient with classic hemophilia as reagent The first method although of confirmed value is time consuming a disadvantage of the second method is that adequate amounts of hemophilic blood are not always easily available Thus an alternative rapid method using readily available materials would be of value The principle of such a method was suggested by observing the effects of disodium ethylenediamine tetra acetic acid (Na EDTA) on certain clotting factors Rapid and pronounced losses of proaccelerin (factor V) and antihemophilic globulin (factor VIII) were the most marked findings

TECHNIC —Normal human blood was collected into Na EDTA (150 mg /100 ml blood) After centrifugation the plasma was de

(1) S e c 129 389 390 F b 13 1959

Prower factor leads to platelet factor 3 which together with factor V and calcium result in blood thromboplastin formation

► [Some skepticism has been expressed concerning the function and even the existence of PTA as a separate entity This article from the laboratory of an expert in the field adds weight to the evidence of its finite properties —Ed]

New Diagnostic and Therapeutic Approach to Fibrinolysis and Hemorrhage was used by J C Heuson W Peers and H J Tagnon[3] (Brussels) in a case in which the plasma during acute fibrinolysis was able to digest a protein substrate different from fibrinogen or fibrin but was markedly inhibited in vitro by soybean trypsin inhibitor (SBI) This is the first attempt to treat fibrinolysis of shock in man by intravenous SBI

Woman 28 had cardiac arrest during cesarean section Cardiac massage restored normal heart action but severe hemorrhagic diathesis with fibrinolysis appeared during the period of shock The plasma digested its own fibrin and a substrate of casein marked with radioactive iodine In vitro addition of SBI inhibited the fibrinolysis She received 300 mg SBI in 150 ml of M/6 sodium lactate followed by 5 Gm human fibrinogen preparation Within 30 minutes bleeding distinctly decreased and a sample of venous blood clotted in 4 minutes but redissolved completely in 30 minutes 2 hours later the redissolving time was 70 minutes A second intravenous injection of 400 mg SBI was given followed 50 minutes later by 5 Gm fibrinogen The plasma no longer was fibrinolytic Subsequently venous blood clotted spontaneously and fibrinolysis did not recur The patient never regained consciousness and died 2 days later

Quantitative evaluation of the intensity of fibrinolysis can be made by measuring the level of fibrinogen in plasma after different lengths of incubation with and without the addition of SBI This method cannot be used if fibrinogen is absent Another more reliable method using I^{131} labeled casein is truly quantitative Measuring the radioactive end products of the reaction of plasma enzymes on casein eliminates any contribution from the plasma to the end product of the reaction Therefore it does not contribute to the blank and readings of the method

Fibrinolysis associated with severe bleeding is an acute emergency immediately threatening the patient s life As long as it persists hemostasis may remain deficient and bleeding continue Large amounts of human fibrinogen seemed successful in a number of cases due to afibrinogene

(3) Blood 13 8 4 88 September 1958

and 52 with moderate PTA deficiency Neither showed spontaneous bleeding but both manifested a definite hemorrhagic tendency after surgical interventions and tooth extractions The diagnosis of PTA deficiency was established by matching studies using the blood of the study patients and of patients with hemophilia A (antihemophilic globulin deficiency) hemophilia B (plasma thromboplastin component deficiency) and known PTA deficiency

One of the authors 2 patients was personally examined by Rosenthal who confirmed the diagnosis of PTA deficiency The most significant features of this patient s clotting defect were prolonged clotting time highly abnormal prothrombin consumption and in a pathologic thromboplastin generation test in which the patient s plasma and serum were used in the same incubation mixture separate substitution of the plasma or serum yielded normal thromboplastic activity The thromboplastin generation test with prothrombin poor PTA deficient serum (obtained by adding brain thromboplastin to whole blood) resulted in decreased formation of thromboplastin

By paper electrophoresis of a concentrate of serum factors a protein fraction could be obtained which contained minimal amounts of all known clotting factors and had a high PTA activity This result suggests that the PTA factor is a separate entity

The serum of the study patients showed reduced factor IX activity as measured with a one stage assay The corrective effect of factor IX deficient plasma or serum on the clotting defect of these patients however was comparable to that of normal plasma or serum

Addition of hemophilia B plasma or serum or of $BaSO_4$ adsorbed plasma or serum (factor IX free) to freshly drawn whole blood of the study patients resulted in significantly higher factor IX levels in serums thus obtained These findings could be explained by the hypothesis that PTA acts on a very early stage of blood thromboplastin formation and is necessary for the activation of factor IX

With the inclusion of the PTA factor the following scheme of enzymatic chain reactions leading to thromboplastin formation is suggested Hageman factor + PTA factor leads to factor VIII this in turn combined with factors IX and X (prephase activator [PPA]) and the Stuart

of antihemophilic globulin Unfortunately this title is vague it has been used for many different clotting abnormalities and there are significant differences between the condition it denotes and hemophilia The best title is antihemophilic *globulin deficiency associated with capillary defect*

Treatment of continued bleeding requires fresh blood—drawn within 2 hours of transfusion—or antihemophilic factor concentrate Faulty capillaries probably cause the prolonged bleeding time

► [See also the last article in the preceding section Thrombocytopenic and Vascular Purpuras —Ed]

Pathologic Anatomy of Macroglobulinemia Waldenstrom was studied by H U Zollinger[5] (St Gallen Switzerland) in 8 patients The macroscopic findings were generally uncharacteristic Common findings were only the bone marrow changes (diffuse reddening) which however are found in many other diseases The spleen was enlarged in 5 patients whereas it was smaller than normal in 1 patient The lymph node findings also varied They were definitely enlarged in 2 patients slightly enlarged in 4 and revealed typical metastases in 1 patient The liver was enlarged in 3 patients the kidneys in 2 Osteoporosis was present in all but 1 patient The macroscopic heart findings were not specific One patient presented hemorrhage in the centrum semiovale whereas the other showed purpura cerebri The triad of splenomegaly enlarged lymph nodes and red bone marrow seems to be characteristic of Waldenstrom s disease The disease is considered to be a myelogenic reticulomatosis with macroglobulinemia

The bone marrow is always affected with microscopic changes of four types In type I the marrow contains almost exclusively typical plasma cells in enormous number The nuclei vary only slightly in size and show mitoses only occasionally In type II only some of the cells are plasma cells The whole picture is multiform and the nuclei show great variation in size shape and chromatin content In type III small lymphoid cells predominate though plasma cells and as in the other types Russell s bodies are also present In type IV the marrow is flooded with polymorph cells among which small lymphoid and atypical plasma cells can be seen

Cortical erosion and involvement of the periosteum was

(5) H l t. med t 25 153 183 M y 1958

min but the fibrinogen is often contaminated with plasminogen and may possibly transmit viral hepatitis A more logical approach to treating hemorrhagic manifestations of fibrinolysis is to stop the activity of the responsible enzyme After the second intravenous SBI injection the plasma proteolytic activity was nil fibrinolysis stopped in vivo and shock was corrected Further use of SBI in the same disorder appears justified to confirm its therapeutic effectiveness

► [*It is hoped that such further work will be done —Ed*]

Bridge Anticoagulant in Willebrand s Syndrome In this *hemorrhagic disease disproportionate bleeding appears from* minor injuries in childhood males and females are equally affected and the bleeding time is prolonged Blood clotting time is normal but the prothrombin consumption test is abnormal and a deficiency of antihemophilic globulin has been proved by the thromboplastin generation test as observed by Alexander and by Singer All patients with true hemophilia or Christmas disease show a blood clotting inhibitor in the plasma This factor is called Bridge anticoagulant after the name of the first patient and seems to be part of the inherited abnormality of the hemophilia syndrome John F Wilkinson F Nour Eldin and M C G Israels[4] (Univ of Manchester) studied 3 patients with the typical history findings and laboratory confirmation of Willebrand s syndrome Thromboplastin generation tests and determination of the clotting times of a citrate plasma substrate using normal or patient s plasma showed that the clotting time with the hemophilic patient s plasma substrate was longer than with normal substrate and the difference was greater if undiluted aluminum hydroxide treated plasma was used in the incubation mixture No such differences from normal plasma were found with the plasma of the 3 patients with Willebrand s syndrome Therefore Bridge anticoagulant was absent

This absence of Bridge anticoagulant distinguishes the coagulation defect of Willebrand s syndrome from both classic hemophilia and Christmas disease and it conforms to the different type of inheritance and the really different clinical picture The name vascular hemophilia *should not be used* Pseudohemophilia seems more suitable because it indicates the resemblance to hemophilia especially the deficiency

(4) Lancet 115 117 July 19 1958

with celontin therapy (1 case) Minnesota Med 42 130 131 February 1959
Holsinger D R Hanlon D G and Welch J S Fatal aplastic anemia following sulfamethoxypyridazine therapy (1 case) Proc Staff Meet Mayo Clin 33 679 681 Dec 24 1958
Kringelbach J Aplastic anemia following chloromycetin treatment of whooping cough (1 case) Ugesk laeger 120 915 916 July 10 1958

Megaloblastic anemia
Calvert R J Hurworth F and MacBean A I Megaloblastic anemia from methophenobarbital (1 case) Blood 13 894 898 September 1958
Chanarin I Elmes P C and Mollin D L Folic acid studies in megaloblastic anaemia due to primidone (1 case) Brit M J 2 80 82 July 12 1958
Montgomery D and Craig J Megaloblastic anaemia during primidone therapy (1 case) Scot M J 3 460 461 November 1958
Stokes J B and Fortune C Megaloblastic anaemia associated with anticonvulsant drug therapy (1 case) chiefly primidone and phenytoin Australasian Ann Med 7 118-125 May 1958

Hemolytic anemia
Brown E H and Bailey E H Acute haemolytic anaemia in case of infantile gastro enteritis treated with oxytetracycline (1 case) Brit M J 2 1204 1205 Nov 15 1958
Levy D and Porgess A Haemolytic anaemia in a child receiving nitrofurantoin (1 case) Arch Dis Childhood 33 527 528 December 1958
Rowland H A K Acute haemolysis following PAS (1 case) Brit M J 2 92 July 12 1958
Sansone G and Segni G Acute hemolytic anemia due to sulfonamide and to PAS Pathogenic differences (1 case) Boll Soc ital biol sper 34 1556-1558 Nov 30 1958
Smith R S and Alexander S Heinz body anaemia due to dapsone (3 cases) Brit M J 1 625 627 Mar 7 1959
Spriggs A E *et al* Heinz body anaemia due to salicylazosulphapyridine (3 cases) Lancet 1 1039 1041 May 17 1958

Agranulocytosis
Adams D A and Perry S Agranulocytosis associated with thenalidine (sandostene) tartrate therapy (3 cases) J A M A 167 1207 1210 July 5 1958
Arora Y C Agranulocytosis following acetazolamide therapy (1 case) New York J Med. 59 1119 1120 Mar 15 1959
Lieber P and Pabst Agranulocytosis induced by therapeutic use of largactil in small doses in senile pruritus Bull Soc franç dermat et syph 65 206-208 Apr May 1958
de Blecourt J J Bode J J and Nagelsmit W F Agranulocytosis after treatment with amodiaquine (camoquin) in patient with disseminated lupus erythematosus Nederl tijdschr geneesk 103 14 16 Jan 3 1959
Borell L R Agranulocytosis following use of nartrate (dipyrone) (1 case) New York J Med 58 3179 3181 Oct. 1 1958
Brachman P S McCreary T W and Florence R Agranulocytosis induced by trimeprazine (1 case) New England J Med. 260 378 380 Feb 19 1959
Fiore J M and Noonan F M Agranulocytosis due to mepazine (phe

seen in 1 instance Involvement of the bone marrow is due to a tumorous transformation of the reticulum and its derivatives Involvement of the lymph nodes varies from patient to patient and even from one node to the other The mast cells are increased in number the structure of the nodes obscured and the follicles unrecognizable Characteristically filtrates break through the lymph node capsule and penetrate into the surrounding fatty tissues

In 4 patients the kidneys showed interstitial infiltrations consisting of lymphoid and plasma cells In the other 4 the kidneys presented a lymphohistioplasmocytic focal interstitial nephritis Glomerulonephrosis appearing as a result of paraproteinemia was a constant finding It has not been described previously in Waldenstrom s disease Myocardosis was observed in 6 patients characterized by edematous broadening of the interstitium without inflammatory cellular infiltration Infiltrations by small lymphoid cells and by mostly typical occasionally atypical plasma cells in the brain were observed in 3 patients and cerebral tumor nodules in 1 patient

DRUG ASSOCIATED BLOOD DYSCRASIAS

This section has been an annual feature since the 1956-57 YEAR BOOK when it was initiated in an attempt to include as many case reports from the world literature concerning the topic as were available or indexed for the period covered by the volume No doubt many similar clinically undesirable effects are not reported especially when the therapeutic agen is not a new one It is to be emphasized that the items for the most part present a chronologic association rather than a proved causality However this may be useful to the physician in weighing the advantages against the possible hazards of a drug in a particular clinical situation Today the multiplicity of effective therapeutic agents available suggests a modification of the ancient injunction Primum non nocere perhaps to First run no therapeutic risk greater than that of the disease —Ed

Aplastic anemia or pancytopenia

Green, R A and Gilbert M G Fatal bone marrow aplasia associated

fatal hemorrhagic purpura in children Bull Acad nat med 142 565 573 June 17 24 1958
Nordqvist, P Cramer G and Bjorntorp P Thrombocytopenia during chlorothiazide treatment (3 cases) Lancet 1 271 272 Feb 7 1959
Platt P Thrombocytopenic purpura apparently due to tablets containing salicylamide and mephenesen (arthripax) (1 case) Brit M J 2 1577 1578 Dec 27 1958
Schen R J and Rabinovitz M Thrombocytopenic purpura due to quinidine (1 case) Brit M J 2 1502 1503 Dec 20 1958
Schwartz M J and Norton W S Thrombocytopenia and leukopenia associated with use of sulfamethoxypyridazine (2 cases) J A M A 167 457-458 May 24 1958

nothiazine) (3 ca es) New England J Med 260 375 378 Feb 19 1959
Giles C and Vereker P Fatal case of agranulocytosis due to chlorpromazine (1 case) Brit. M J 2 289 290 Aug 2 1958.
Grace W J Thrombocytopenia in patient taking chlorpropamid (1 case) New England J Med 260 711 712 Apr 2 1959
Hippius H and Kanig K Agranulocytosis due to neuropsychiatric phenothiazine therapy Arztl Wchnschr 13 501 507 June 6 1958
Kjeldsen M H Agranulocytosis following phenylbutazone therapy (1 case) Ugesk laeger 120 916-918 July 10 1958
Kreisle, J E. Agranulocytosis during promazine (sparine) therapy (1 case) Texas J Med 55 297 300 April 1959
Larrain C and Jimenez L Agranulocytosis following use of chloramphenicol Rev med Chile 86 646 649 October 1958
Madsen K A and Thomsen N J Agranulocytosis caused by amidopyrine (1 case) Ugesk laeg r 120 918 920 July 10 1958
Maurel H Nitzan L and Spielmann J P Fatal agranulocytosis during chlorpromazine therapy (1 case) Ann med psychol Paris 116 156 159 June 1958
Petersen M C Carey B and Rhoads D V Blood dyscrasias due to phenothiazine derivatives (4 cases) Am J Psychiat. 115 25 258 September 1958
Pisciotta A V et al Agranulocytosis following administration of phenothiazine derivatives (18 cases) Am J Med 25 210 222 August 1958
Rich M and Belle M S Agranulocytosis resulting from methimazole (tapazole) (3 cases) J A M A 167 573 575 May 31 1958
Tuteur W Kent G and Stiller R Agranulocytosis and jaundice following chlorpromazine therapy (1 case) Illinois M J 114 234-238 November 1958
Vetne G Granulocytopenia associated with chlorpromazine therapy (6 cases) J Michigan M Soc 57 709 710 May 1958
Wendenroth H and Balzereit F Two cases of agranulocytosis after sulfonamide therapy of diabetes Med. Klin Berlin 53 1560 1561 Sept. 5 1958
Zolov B Agranulocyto is resulting from sandostene (1 case) J Main M A 49 335 337 September 1958
Zucconi V and Balestra F Two cases of agranulocytosis due to phenylbutazone Rass gиl Med Trieste 14 180 182 October 1958.
Zuckerman A J and Chazan A A Agranulocytosis with thrombocytopenia following chlorothiazide therapy (1 case) Brit. M J 2 1338 November 29 1958

Purpura

Day H J Conrad, F G and Moore J E Immunothrombocytopenia indu ed by novobiocin (1 case) Am J M Sc. 236 475-481 October 1958
Hazlett, B E and Yendt E R Thrombocytopenia following gold therapy with successful treatment (1 case) Canad M A J 79 31 33 July 1 1958
Horowitz H I Shapiro B and Rubin I L Athrombocytopenic purpura caused by chlorothiazide (1 case) New York J Med 59 1117 1118 Mar 15 1959
Jaffe M O and Kierland R R Purpura due to chlorothiazide (diuril) (2 cases) J A M A 168 2264 2265 Dec 27 1958
Kirchmair H Thrombopenia in doriden therapy (1 case) Med. Klin Berlin 53 1683 1684 Sept. 26 1958.
Lamy M et al Dangers of chloramphenicol therapy Three cases of

The Heart *and* Blood Vessels *and* The Kidney

TINSLEY R HARRISON MD

PART IV

THE HEART AND BLOOD VESSELS AND THE KIDNEY

CONGENITAL HEART DISEASE

Localization of Circulatory Shunts with Inhaled Krypton 85 Preliminary Clinical Report is presented by Richard J Sanders and Andrew G Morrow[1] Use of a radioactive inert gas provides the sensitivity of the nitrous oxide test but substitutes a rapid and simple counting procedure for the laborious manometric analysis necessary with nitrous oxide

METHOD —With the tip of the catheter in the pulmonary artery and a needle in a femoral or brachial artery the patient hyperventilates a mixture of 0 1 0 4 mc Kr^{85}/L air administered from a spiromet r through a closed system After breathing for 30 seconds the patient breathes room air and the exhaled air containing the radioactive gas is collected in a Douglas bag for the next 5 minutes Then 2 cc samples are drawn simultaneously from the catheter and the needle at various intervals during the 30 seconds of inhalation The Kr^{85} content is analyzed If results of the pulmonary artery test indicate a shunt the test is repeated in the right ventricle and right atrium to localize it

In controls the highest Kr^{85} sample in mixed venous blood was 16% and most were under 10% of the systemic arterial sample Among patients with a left to right shunt when the catheter was distal to the point of the shunt 22 of 24 tests showed a ratio over 20% and the other 2 tests both in patients with small atrial septal defects showed 16 and 19%

The Kr^{85} test correlated well with the N_2O test In most the ratios differed by only a few per cent Oxygen determinations however were misleading or inconclusive in 5 of the 17 patients compared The limitations of the oxygen method are attributable to the variable oxygen content of mixed venous blood associated with changes in the metabolic state and to difficulty in obtaining representative samples from the

(1) B ll Joh H pk H p 103 27 31 J ly 1958

CASE 2—Girl 18 had moderate cyanosis since birth AQRS was located near +140 degrees (sextant IV of Bayley) These malformations had to be considered Fallot s tetralogy Fallot s trilogy Ebstein s disease transposition of the great vessels Fallot s pentalogy and common trunk The advanced degree of right bundle branch block implied Ebstein s disease The qR type complexes with negative T waves in V_1 and V and qRs complexes with negative or diphasic T waves in V_3 V_4 and V_5 suggested pronounced right auricular dilatation Absence of unipolar morphologies belonging to the right ventricle the high and wide P waves in leads I and II all suggested Ebstein s disease as found at autopsy

Interauricular Communications with Reference to 81 Cases are discussed by P Soulie J Carlotti F Joly J Acar and J Forman[3] In 13 cases the septal defect was associated with other cardiopathy In the other 68 cases (48 females) in which the interauricular communication was the only anomaly diagnosis of the septal defect was verified anatomically in 11 (in 4 at autopsy and in 7 at operation) and by hemodynamic study in 57 (catheterization in 41) Age range was 7 57 years (average 25)

Hemoptyses were rare and syncope was relatively frequent Cyanosis was present in association with pulmonary hypertension and increased pulmonary resistance It is rarely observed in a young patient without cardiac failure and is evidence of a massive venous arterial shunt It is present as a rule in adults with cardiac insufficiency complete arrhythmia and cardiac enlargement thus indicating peripheral stasis rather than reversed shunts Pregnancies had been well tolerated Of 30 pregnancies in 12 women 27 proceeded to term with 26 normal infants (1 stillborn) Three pregnancies were interrupted before the 6th month but it could not be determined whether the abortions were spontaneous or induced

Systolic murmur (90%) and splitting of the 2d heart sound in the pulmonary area (82%) were the most frequent auscultatory signs A diastolic murmur was present in 30% of cases this is due to wide communications with a large heart and pulmonary hypertension The mechanism of diastolic murmurs can be related directly to the shunt or to pulmonary insufficiency or relative tricuspid stenosis Signs of congestive cardiac insufficiency i e mild right ventricular insufficiency were present in 19 1% of cases

Cardiac insufficiency is apparently due to two causes (1)

(3) S m b p F 35 669 708 F b 8 1959

venae cavae Inhalation of an inert gas such as Kr^{85} or N_2O results in a large difference between the arterial and venous levels of the gas independent of the metabolic state In addition since the inert gas content of mixed venous blood in patients without left to right shunts never exceeds a fixed percentage of the arterial content (15% for N O) it is possible to establish presence or absence of a shunt without sampling vena caval blood The Kr^{85} test criteria approximate those for N_2O and estimation of the magnitude of the left to right shunt should be possible by application of the mixing formula described for the N O test

Mean Manifest Electric Axis of Ventricular Activation Process (AQRS) in Congenital Heart Disease New Approach in Electrocardiographic Diagnosis Demetrio Sodi Pallares Fulvio Pileggi Fernando Cisneros, Paulo Ginefra Bolivar Portillo Gustavo A Medrano and Abdo Bisteni[2] (Mexico City) studied 1 331 ECG s corresponding to congenital heart cases focusing special attention on the AQRS position This position was determined by measuring positive and/or negative areas enclosed within the deflections Bayley s triaxial system was used to plot and study axial distribution The combination of the determination of AQRS in the frontal plane with knowledge of the ECG pattern of each congenital heart malformation permitted the main diagnosis of the anomaly in many patients 2 patients are described

CASE 1—Boy 8 had marked cyanosis since birth AQRS was located around −135 degrees (sextant III of Bayley) In this sextant these malformations should be considered in diagnosis Fallot s tetralogy Fallot s trilogy persistent common atrioventricular canal Ebstein s disease single ventricle and transposition of the great vessels Evidently some can be discarded Ebstein s disease (high R waves in V_1 and V and absence of right bundle branch block rule out this possibility) transposition of the great vessels (T wave behavior makes this possibility improbable) persistent common atrioventricular canal (improbable diagnosis because of absence of right bundle branch block and lack of left ventricular enlargement) and single ventricle (absence of predominance of negative and isodiphasic complexes adds to improbability of this diagnosis) Presence of deeply negative T waves from V_1 through V_3 pronounced displacement with upward concavity of the RS T segment in the standard leads V_5 and V_6 and presence of qrS type complexes in leads I V_5 and V_6 speak more in favor of the trilogy than of the tetralogy of Fallot Diagnosis of Fallot s trilogy was proved at autopsy

(2) Am H t J 55 681 700 M y 1958

ance also must be considered Pulmonary capillary pressure was increased in 25% of cases and pulmonary arterial hyper ten ion observed in 50% It is usually moderate principally systolic and related to the increase of pulmonary deficit More rarely pulmonary hypertension is severe pertaining to both systolic and diastolic pressure and accompanies in creased pulmonary resistance with variable functional insuf ficiency Pulmonary arterial resistance although not con stant increases with age especially after 40 years This increase is related to anatomic changes in the pulmonary ar teriolar bed involving muscular arteries and arterioles Com parison of pulmonary arterial and venous pressure curves obtained by catheterization in vivo provides useful infor mation regarding the condition of the pulmonary vascular bed

Clinical radiologic ECG and hemodynamic findings per mit classification of septal defects into three main groups representing different stages of progression In stage I pul monary arterial pressure is normal in stage II it is in creased but pulmonary arteriolar resistance is normal in stage III there is pulmonary hypertension with increased pulmonary arteriolar resistance Ideally operation for re pair of the septal defect should be performed during the first two stages because organic and functional changes in crease the surgical risk in more advanced cases Neverthe less operation is sometimes indicated because of progression of pulmonary hypertension and cardiac signs In 1 patient operated on at age 45 under such conditions postoperative results were excellent

Electrocardiogram in Interatrial Septal Defects and Its Correlation with Hemodynamics The pattern of incomplete right bundle branch block is frequent in patients with an in teratrial septal defect This probably is not a disturbance in conduction in the right branch of the bundle of His but rather in the basal portions of the free wall of the right ventricle and perhaps the higher parts of the interventricular septum Jorge Martins de Oliveira and Henry A Zimmerman[4] (St Vincent Charity Hosp Cleveland) studied 44 patients who had proved interatrial septal defects of whom 32 were op erated on

Duration of the QRS complex was 0 055-0 11 second No

(4) Am Heart J 55 369 382 M h 1958

severe pulmonary deficits with large arteriovenous shunts without pulmonary hypertension which apparently are responsible for the decompensation and conversely (2) severe pulmonary hypertension Aside from these conditions cardiac insufficiency is characterized by inconstant cyanosis frequency of complete arrhythmia persistence of an exclusively or predominantly arteriovenous shunt and a large increase in the filling pressure of the right ventricle Myocardial insufficiency in the individual case of septal defect cannot be classified on the basis of hemodynamic findings alone Most patients without clinical signs of ventricular failure have elevated right ventricular telediastolic pressure

Radiologically changes in the pulmonary arterial tree (increase in size expansion) provide a reliable sign of interauricular communications The heart is consistently increased in size in cases in which a severe pulmonary deficit is associated with pulmonary hypertension Pulmonary arterial calcification is rare but appears to be a definite indication of pulmonary hypertension

Electrocardiographic changes are acquired and increase with progression duration of QRS increases with age There is some correlation between hemodynamic and ECG changes the amplitude of R or R in V_1 depends on two factors of right ventricular surcharge—pulmonary arterial hypertension and increase of pulmonary deficit The incidence of right bundle branch block is high (80%) a complete right block supervenes in an advanced stage of cardiopathy Hemodynamic studies show that the rSR in V_1 of right branch block does not necessarily indicate a ventricular asynchronism probably it results from right ventricular hypertrophy Postoperative ECG findings accurately reflect the effectiveness of operation ECG anomalies may regress soon after surgery

Pulmonary venous saturation is normal in most cases severe bronchopathy with respiratory insufficiency is rare Shunts are mixed in over half the cases factors controlling shunts are complex A study of pressure curves recorded simultaneously in both atriums demonstrates that the working of the pressures at the auricular level is not sufficient to explain the direction of the shunts The situation type and size of the septal opening distensibility of the two ventricles and respective levels of pulmonary and systemic arte[illegible] I resist

bear on the patient s ability to survive the operative period It was found that a clinical history of congestive heart fail ure a markedly elevated right atrial pressure a large right to left shunt severely elevated pressure in the pulmonary ar tery and markedly increased pulmonary vascular resistance adversely affect the operative risk in the group as a whole If none or only one of these unfavorable factors exists in a given patient the risk of operation is highly acceptable The risk is very high when two such factors are present and appears ex treme if three or more coexist Age per se did not appear to influence operative mortality strongly

Closure of atrial septal defects in patients in whom pul monary blood flow is clearly less than systemic blood flow will almost always result in death The same appears true for patients with patent ductus arteriosus aorticopulmonary fis tula common atrioventricular canal and ventricular septal defect

Once chronic heart failure from whatever cause has oc curred the ability of the heart to regain compensation is ap parently hampered since any tendency to do so again in creases the volume of the left to right shunt and thus the work of the right ventricle Therefore in certain patients it would seem inordinately difficult for the right ventricle to recover from a state of chronic failure for not only is it un able to escape the burden of any existing pulmonary hyper tension but also as it might tend to regain compensation the volume load imposed on it is increased This does not pertain to acute heart failure due to severe arrhythmia to which these hearts are prone and which may quickly subside with the return of normal rhythm

The mortality rate for repair of uncomplicated atrial sep tal defects by the atrial well technic was less than 2% Be cause of this low operative risk it is suggested that an atrial septal defect of significant size be repaired by this method even in the asymptomatic or minimally symptomatic patient

Ostium Primum Syndrome was studied by Brian Kiely Paul Adams Jr Ray C Anderson and Richard G Lester [6] When there is abnormal development of the atrioventricular endocardial cushions in fetal life four congenital cardiac le sions may result persistent ostium primum cleavage of the aortic cusp of the mitral valve cleavage of the septal cusp of

(6) A.M A J D Ch ld 96 381-403 Sept mbe 1958

patient had so called complete right bundle branch block A late R (R) wave was present in lead V_1 in 34 (77%) In 9 (20%) there was an initial R followed by an S wave in 6 Hypertension of the lesser circulation was marked in 3 of these moderate in 3 and 3 were normal In the absence of an R or RS pattern in V_1 right ventricular pressure was not usually elevated However an R or RS pattern could be present even if pressures were not elevated

No patient with a shunt flow below 30% had a late R (R) wave in V_1 The more the magnitude of the shunt flow increased the more the pattern of RSR was found Those with large shunt flows had a proportionate increase in the height of the R wave

Twelve patients had open heart surgery and postoperative ECG s within 8 40 days In 8 (67%) the vector of auricular activation tended to deviate to the left in the frontal plane and in 10 (83%) to deviate backward in the horizontal plane indicating correction of the septal defect In 10 patients the mean axis of ventricular activation showed lesser deviation to the right in the frontal plane which may correspond to a diminution of dilatation of the right ventricle reflecting a decrease in overloading In the 11 patients who had had a late R (R) wave in V_1 before operation 9 showed a decrease in its voltage and in 2 it disappeared entirely after surgery Among 7 with a late S (S) wave it completely disappeared in 5 voltage decreased in 1 and in 1 it remained the same

The RSR or RSR S pattern in right precordial leads apparently means anatomic changes in the basal regions of the right ventricle and the higher parts of the interventricular septum due to dilatation and hypertrophy The small number of Purkinje fibers in this region leads to slowing of the wave of depolarization When the entire right ventricle hypertrophies the basal regions no longer predominate and the ECG pattern of concentric hypertrophy is superimposed giving ri e to the R or RS morphology

Atrial Septal Defect Factors Affecting Surgical Mortality Rate Dwight C McGoon H J C Swan Robert O Brandenburg Daniel C Connolly and John W Kirklin[5] (Mayo Clinic) studied the data on 119 adult patients who had been operated on for closure of an atrial septal defect and tried to determine what features determinable preoperatively

(5) C rcul t n 19 195 00 Febru ry 1959

cardiopulmonary bypass with the Melrose N E P pump oxygenator The patients were aged 2½ 25 with average age of 8¼ Of these patients 4 had in addition patent ductus arteriosus Of the 15 patients with a ventricular defect as the sole lesion only 1 died Among the 4 with an additional patent ductus 2 died One patient with two defects also died but 1 with a single ventricle survived

Of the 20 patients whose defects were closed the right ventricular systolic pressure as a percentage of the left after closure was nearly normal in 5 slightly elevated in 8 moderately raised in 3 and high in 4

About 3 6 weeks after operation all were active and well Exercise tolerance was improved in most Jugular venous pressure and pulse were normal in all but 1 The thrill and murmur of the ventricular defect disappeared in all and in only 2 did a mitral diastolic murmur persist Soft or moderate ejection systolic murmurs at the left sternal edge were common postoperatively and probably originated in the infundibulum or pulmonary artery they were sometimes best heard near the apex Basal diastolic murmur persisted in 4 In most patients the ECG showed a constant unusual pattern There was complete right bundle branch block with the secondary R wave persisting as far as V_5 V_6 together with striking T wave inversion in all chest leads These appearances were presumably due to the intracardiac maneuver and the ventriculotomy

In assessing patients for operation the main problems are detection of additional lesions and prediction as to whether good hemodynamic response will result from closure

Pulmonary Stenosis with Left to Right Shunt With Special Reference to Its Clinical Diagnosis Such cases are not rare Several papers have described this finding and 5 more cases are reported by Kalevi Pyorala and Sven Punsar[8] (Helsinki) Diagnosis is difficult before cardiac catheterization Symptoms are mild or absent Cyanosis and clubbing are usually absent If pulmonary stenosis is severe slight cyanosis may occur especially after exercise If the shunt is at the ventricular or atrial level a loud systolic murmur is best heard at the 2d and/or 3d left interspace usually accompanied by a thrill and transmitted toward the left clavicle A

(8) A med t Fen 47 83 104 1958

the tricuspid valve and deficiency of the membranous inter ventricular septum About 11 different combinations of these lesions have been reported and others may be possible The most important combinations are persistent common atrio ventricular canal in which all four lesions are present and ostium primum with cleft mitral valve

Isolated ostium primum is rare The presence of associated abnormalities usually cleavage of the aortic cusp of the mi tral valve probably contributes greatly to the poor surgical risk in patients with this defect When ostium primum is present at least in ostium primum with cleft mitral valve and atrioventricular canal a characteristic syndrome is pro duced that makes it possible to distinguish defects associated with ostium primum from other types of interatrial and in terventricular septal defect Characteristic features are sys tolic thrill apical systolic murmur diastolic murmurs prolonged P R interval left axis deviation with right ven tricular hypertrophy horizontal heart by ECG left ven tricular and left atrial enlargement on x rays interatrial shunt by catheterization and pulmonary hypertension

Differentiation of ostium primum with cleft mitral valve and persistent atrioventricular canal from most other types of congenital heart disease is usually possible by applying the 10 criteria Other conditions that are most difficult to dis tinguish from these two are Lutembacher s syndrome and interatrial defect other than ostium primum plus interven tricular septal defect Ostium primum with cleft mitral valve cannot yet be distinguished from atrioventricular canal unless catheterization shows arterialization in the atrium and ventricle Little is known about the findings in the many rarer combinations of lesions associated with ostium primum

Treatment of Ventricular Septal Defect is evaluated by W P Cleland A J W Beard H H Bentall M B Bishop M V Braimbridge L L Bromley J F Goodwin A Holl man W F Kerr E B Lloyd Jones D G Melrose and L J Telivuo (Postgrad Med School London) Because few patients with ventricular septal defect survive past the 3d decade all with a moderate sized to large defect should be considered for surgery The authors studied 21 patients with ventricular septal defect who were operated on under total

(7) B t M J 2 1369 1377 D c 6 1958

slight cyanosis of the lips and acra. Chest x rays showed the right half of the chest which contained the heart to be smaller than the left half. The ECG did not indicate true dextrocardia. Tomograms of the retrocardiac lung sections revealed vascular shadows in shrublike arrangement which branched off dichotomically. Increasing in width craniocaudad they converged to one point at the diaphragmatic shadow and submerged there. In most tomographic depths a button shaped deformity of the pulmonary artery was seen from which only a few small branches took off into the periphery. At 12 cm there was a nonhomogeneous triangular shadow in the lateral area of the right lower lung field. This shadow was also connected with some vascular markings which disappeared into the diaphragmatic area at a point other than the vessels mentioned.

These findings together with the results of bronchographic cardiac catheterization and pulmonary function studies indicated the following pathologic conditions: anomalous pulmonary veins apparently draining the entire right lung into the inferior vena cava, veins carrying fully arterialized blood into the vena cava, heart in dextroposition and presenting an atrial septal defect with predominantly right-to-left shunt, hypoplasia of right pulmonary artery and of right lower lobe with hypoplastic bronchi and segmental bronchi ending blind, an oversized right upper lobe, distinct limitation of functional capacity of right lung and suspicion of the presence of an extra lung with direct aortal blood supply.

Anomalous pulmonary veins may be suspected when the heart is dislocated to the right, when the right hemithorax is smaller than the left and when an unusual saber-like density is visible along the right heart or within the heart shadow. In childhood a partially anomalous venous drainage usually causes serious disturbances only if accompanied by an atrial septal defect. Life expectancy depends on the number and total diameter of the aberrant veins and on the concomitant cardiac and pulmonary anomalies.

Coronary Arteriovenous Aneurysm. Review of Literature with emphasis on a particular case is presented by Jeppe Schultz[1] (Univ. of Aarhus). Most arteriovenous coronary aneurysms are undoubtedly congenital anomalies. Only rarely are they a sequela of spontaneous rupture of a simple congenital coronary aneurysm. In embryonic life the coronary arteries communicate with the veins through an ordinary capillary network. The arteries give off branches to the intratrabecular spaces, the sinusoids, which communicate with the ventricular cavities. Later the sinusoids shrink into a normally calibrated capillary network and the communication with the cavities becomes the thebesian veins.

(1) Am. Heart J. 56:431-442, September, 1958.

murmur typical of pulmonary stenosis may be recognizable at the 2d left interspace and a lower plateau shaped systolic murmur of ventricular septal defect Finding a thrill at the pulmonary area in cases which are otherwise typical of atrial septal defect should suggest coexistent pulmonary stenosis because a thrill is rare in uncomplicated atrial septal defect

In solitary pulmonary stenosis the pulmonary component of the 2d sound is delayed because of the lengthening of right ventricular systole The intensity of the pulmonary component diminishes as the pulmonary stenosis becomes more severe These findings are the same in cases with left to right and right to left shunts if the gradient corresponds

The ECG findings were mentioned in 85 reported cases in the literature Right ventricular hypertrophy was found in 41 patients left ventricular hypertrophy in 3 combined ventricular hypertrophy in 8 incomplete right bundle branch block in 5 complete right bundle branch block in 6, incomplete right bundle branch block and right ventricular hypertrophy in 12 atrioventricular dissociation and auricular fibrillation in 1 and normal findings in 9 The findings may resemble those of uncomplicated ventricular or atrial septal defect and sometimes those of typical pulmonary stenosis

X ray examination usually shows increased vascularity of the lungs sometimes associated with hilar dance The pulmonary artery and its main branches may show poststenotic dilatation especially in patients with atrial septal defects in whom the stenosis is usually valvular Concavity of the infundibular region associated with pulsatile hilar shadows should suggest infundibular pulmonary stenosis with left to right shunt

Diagnosis is confirmed by cardiac catheterization Angiocardiography may also be diagnostic Dye dilution curves during cardiac catheterization may demonstrate small right to left shunts or verify anomalous pulmonary venous connections

Anomalous Drainage of Pulmonary Veins into Vena Cava Inferior Report of Case is presented by F Longin and G Peppmeier[9] (Univ of Wurzburg)

Woman 48 had had exertional dyspnea since early childhood At 30 she had severe attacks of hemoptysis Before that she had had 2 normal deliveries and 2 miscarriages Physical examination revealed

(9) Fortsch G b R ntg st hlen 88 386 400 Ap 1, 1958

with the right ventricle in 4 patients aged 14 months to 18 years Aneurysms of the coronary arteries may be congenital or acquired The diffuse aneurysm with an arteriovenous communication is considered congenital in origin and is most commonly found involving the right coronary artery In 2 of the patients the right coronary artery with diffuse aneurysm communicated directly with the right ventricle In the boy aged 14 months the large right coronary artery emptied into an aneurysm at the apex of the right ventricle The communication of the large anomalous branch of the left coronary artery with the outflow tract of the right ventricle was not associated with an aneurysm of the artery or ventricle These anomalies are believed to be congenital The history of 3 patients (aged 14 months to 9½ years) revealed cardiac murmurs heard at age 1 1½ and 7 months respectively which were noted from 1 36 months before surgery Development was normal in each 1 was considered slightly undernourished All showed cardiac enlargement and a machinery murmur was heard at the apex or to the right of the sternum in each Catheterization studies revealed a left to right shunt into the right ventricle Angiocardiograms and aortograms localized the lesions which were diagnostic in 2 patients and showed a ruptured sinus of Valsalva in 1 Angiocardiographic studies were not done on the anomalous left coronary artery and it was believed to be a patent ductus arteriosus before operation In all 4 patients the fistulas were closed and the aneurysms resected All have normal cardiac function

Aneurysms and arteriovenous fistulas throughout the body are hazardous and present a serious problem Some patients have been reported living 60 70 and 87 years without cardiac difficulties whereas others have died early in life as a result of infection at the fistula site or rupture of the aneurysm or both

Eisenmenger Syndrome Or Pulmonary Hypertension with Reversed Central Shunt. The distinguishing feature of this syndrome is not the anatomy of the defect but the behavior of the pulmonary circulation Paul Wood[3] (Brompton Hosp London) defines it as pulmonary hypertension with reversed or bidirectional shunt at aortopulmonary ventricular or atrial level It may be caused by patent ductus

(3) B r M J 2 701 709 S pt 20 755 762 S pt 27 1958

The coronary arteriovenous aneurysm represents a preserved fetal communication

In only 2 of the 14 reported cases did the arteriovenous fistula arise because of rupture of a pre existing coronary aneurysm Distribution of the communication was from the right coronary artery to the right ventricle in 1 to the coronary sinus or cardiac veins in 4 and to the right atrium in 3 from the left coronary artery to the right ventricle in 4 to the right atrium in 1 and to the pulmonary artery in 1 Of the 14 5 were diagnosed at operation and 4 were ligated The other 9 were diagnosed at autopsy

Boy 11 had a normal delivery but his mother had severe German measles during the early months of pregnancy Blindness in the right eye had been noted at age 4 weeks and heart murmur at age 3 or 4 years Since he began walking he had a tendency to some dyspnea and fatigue on exertion Examination revealed microphthalmia cataract in the right eye and perceptive deafness of the left ear A slight precordial bulge and palpable thrill at the apex were noted A harsh continuous murmur maximum around the 2d heart sound was heard in the upper precordium with maximum intensity of grade 3 4 in the 2d intercostal space about 2 cm to the left of the sternal margin In the 4th left intercostal space the diastolic component became harsher and the systolic component fainter The 2d pulmonary sound was accentuated

The ECG was normal Chest x ray showed slight enlargement of the left atrium At cardiac catheterization blood samples showed an arteriovenous shunt in two sites viz from the left side to the pulmonary artery and from the left side to the right ventricle The tip of the catheter in the pulmonary artery could be placed in a position where a mixed pulmonary artery and aortic pressure curve could be obtained At operation a patent ductus was found A bulge on the heart was caused by an aneurysm of the branch of the left coronary artery which entered the right ventricle These vessels were ligated and the aneurysm was obliterated

Prognosis is relatively favorable even if no treatment is given Since the anomaly is usually accidentally disclosed at thoracotomy surgical closure seems reasonable if the fistula can be exposed and ligated without too much difficulty and without risk of interrupting the normal coronary circulation Surgery is not indicated for simple aneurysms on the surface of the heart or in its intramural structures

Surgery for Congenital Coronary Artery Arteriovenous Fistulas Egbert H Fell Milton Weinberg Jr Archer S Gordon Benjamin M Gasul and Frank R Johnson (Chicago) observed anomalous coronary arteries communicating

(2) A M A A ch Su g 77 331 335 S pt mbe 1958

murmur a palpable and sharply accentuated pulmonary com ponent of the 2d heart sound and often a loud pulmonary diastolic murmur The characteristic venous pulse and aus cultatory signs of tricuspid incompetence may complicate the picture

The ECG shows a normal or rather prominent P wave and usually moderate or considerable right ventricular prepon derance Skiagrams reveal conspicuous dilatation of the pul monary artery slight to moderate cardiac enlargement and peripheral vascular markings that are usually oligemic but which may be normal or even slightly plethoric

During cardiac catheterization the catheter passed through the defect in 90% of the ducts one third of the aorto pulmonary windows 28% of ventricular septal defects and two thirds of atrial septal defects In cases where the catheter entered the left atrium pulmonary venous samples were fully saturated proving that pulmonary factors do not con tribute to the cyanosis of the Eisenmenger syndrome Pul monary capillary venous pressure was uniformly low and pulmonary vascular resistance high ranging from 800 to 3 600 dynes sec /cm

The physiopathology of Eisenmenger s syndrome lies in the behavior and structure of the pulmonary circulation in the fetus the newborn and during the first 3 months of in fancy The fantastic resistance of the fetal pulmonary circu lation is attributed to the contorted state of the vessels in fully collapsed lungs The thick muscular arteries of the fetus and newborn represent a functional and structural reaction to high pressure Expansion of the lung after birth unfurls the pulmonary vessels and lowers the resistance precipi tously to around systemic level (about 100 units) Subse quent reduction of pulmonary artery pressure is gradual and depends on the relaxing effect of an increased alveolar oxygen tension on vasomotor tone inhibition of vasomotor tone that results from a fall in pressure per se early closure of the ductus preventing an adverse hyperkinetic factor and grad ual involution of the muscular pulmonary arteries In Eisen menger s syndrome with aortopulmonary or interventricular shunt this favorable cycle is prevented by a powerful hyper kinetic factor which maintains the pulmonary artery pres sure at systemic level Vasoconstrictor tone is then not in hibited and the muscular pulmonary arteries do not involute

aortopulmonary septal defect persistent truncus transpos tion with ventricular septal defect corrected transpositio with ventricular septal defect ventricular septal defect sin gle ventricle common atrioventricular canal persister ostium primum atrial septal defect single atrium and hem anomalous or total anomalous pulmonary venous drainag into the right side of the heart

A consecutive series of 127 cases were observed repr senting 8% of the first 1 000 cases of congenital heart disea: seen Autopsies in 53 cases proved conclusively that tr Eisenmenger reaction is excited only by large commun cations between the two circulations The minimal size ‹ aortopulmonary ventricular and atrial communications wa 0 7 1 5 and 3 cm respectively In the absence of the Eiser menger reaction defects of this order result in pulmonar blood flows ranging between 15 and 30 L/minute ‹ pulmonary systemic flow ratios of 3 5 6

The Eisenmenger syndrome occurred in over half the pa tients with aortopulmonary or ventricular communicatior but in only 9% of those with large atrial septal defects I started in infancy in about 80% of patients with patent ductu and ventricular defects but in only 8% of those with atri: septal defects It started in adult life in only 2% of patient with ventricular septal defects but in 92% of those wit atrial septal defects This confirms the hypothesis that th high pulmonary vascular resistance in atrial septal defect i acquired Conversely a high pulmonary vascular resistanc in most cases of patent ductus and ventricular septal defec seems established at birth or at the latest in infancy

The chief symptoms of the syndrome are angina pector: syncope hemoptysis and congestive heart failure Cyanosis clubbing of the fingers and polycythemia are most pro nounced with ventricular shunts and least pronounced wit patent ductus All patients have central cyanosis clubbing polycythemia and breathlessness on effort usually datin from infancy or early childhood Recurrent hemoptysis be gins in adult life and may prove fatal Physical signs com mon to all groups include a small or normal pulse norma venous pressure with or without slight dominance of the ‹ wave an impalpable left ventricle a slight or moderate lif over the right ventricle and pulmonary artery a loud pulmo nary ejection click followed by a short pulmonar systolic

universally fatal congenital heart disease Flow in the aberrant artery has usually been assumed to be from the pulmonary artery to the myocardium and efforts at surgical correction have been directed at increasing the perfusion pressure or oxygen content of pulmonary artery blood Pathologic studies show the aberrant vessel to be thin walled and grossly veinlike Histologically the structure is arterial but with medial atrophy The left ventricle is dilated and there is frequently thinning with scarring of that portion of the left ventricle supplied by the anterior descending coronary artery Other portions of the myocardium are hypertrophied The endocardium of the left ventricle is usually thick resembling endocardial fibroelastosis

Robert B Case Andrew G Morrow Wendell Stainsby and John O Nestor[4] (Nat l Inst of Health) established the diagnosis in 2 infants ante mortem with the help of selective angiography One died during attempted surgical stenosis of the pulmonary artery Postmortem perfusion of the heart showed free communication between the left and right coronary arteries near their origins and the rapidity and profusion of flow into the pulmonary artery suggested that the path of least resistance to flow from the right coronary artery was into the pulmonary artery rather than into the myocardium During life oxygenated blood probably passed via the extensive anastomotic channels from the right coronary artery into the left and then retrograde into the pulmonary artery

Thus although there is oxygenated blood in the left coronary artery it does not reach the myocardium but passes instead into the low resistance circuit of the pulmonary artery Hence it would appear that ligation of the aberrant vessel at its origin would prevent retrograde flow and allow perfusion of the left ventricle by blood supplied through the anastomoses from the right coronary artery This would in effect convert the anomaly into that of a single coronary artery arising from the aorta and supplying both ventricles Thus far 3 patients have had this operation—2 died and 1 is still alive but follow up is too short

Most infants with this anomaly die within the 1st year of life All should be operated on as soon as the diagnosis is established The procedure of choice is temporary occlusion of

(4) C 1 t 17 106 1068 J 1958

Obliterative pulmonary vascular disease due to reactive endarteritis fibrosa is secondary and rarely found in infancy Thrombo obstructive lesions are relatively late and may not be demonstrable before adulthood

The different behavior of atrial septal defect may be explained by the relatively slow involution of the right ventricle after birth The pulmonary vascular resistance may well fall to normal before right ventricular diastolic tone is reduced sufficiently to allow a critical interatrial shunt Once resistance is truly normal flows up to 24 L /minute do not cause pulmonary hypertension

Medical treatment aims at preventing secondary thrombo obstructive lesions by means of permanent anticoagulants Pulmonary vasodilators such as tolazoline aminophylline and reserpine do not lower the pulmonary vascular resistance and do not influence the disease course Small venesections may help in gross polycythemia Heart failure requires the usual remedies Direct repair of a defect without special preparation is justified only when the pulmonary blood flow is at least twice the systemic flow at rest and the pulmonary vascular resistance does not exceed 10 units (800 dynes sec /cm)

The evidence that pulmonary stenosis protects the pulmonary circulation from developing obliterative endarteritis is overwhelming In patients with Eisenmenger s syndrome artificial stenosis of the pulmonary artery may be created surgically to lower the pulmonary artery pressure and so initiate the involutionary cycle The question of how long to maintain the stenosis before repairing the defect is undecided but a year or two should suffice

► [The development of cardiac surgery during the past 15 years has led to a worldwide increase in interest in congenital heart disease New diagnostic methods have been developed and redefinition of the significance of clinical findings has occurred The large number of additional types of congenital heart disease which have been described has tended to bewilder the physician who sees only an occasional such patient This publication by a distinguished British clinician has the great virtue of tending to simplify a subject which has rapidly grown more complex The point of view of the author while unconventional in its application of the term Eisenmenger syndrome has another virtue It places emphasis on the physiology of the circulation rather than on the specific anatomic abnormality —Ed]

Anomalous Origin of Left Coronary Artery Physiologic Defect and Suggested Surgical Treatment Origin of the left coronary from the pulmonary artery is a rare and almost

which the pericardium was not disturbed nor was it found in patients in whom a small segment of pericardium was clamped to permit removal of a pericardial cyst

Since the condition appeared after pericardial incision with or without cardiotomy or valvotomy the term post pericardiotomy syndrome is suggested

The syndrome is interpreted as a traumatic pericarditis possibly a reaction to blood in the pericardial sac Its occurrence in nonrheumatic subjects is a compelling argument against the concept that in patients with mitral valvotomy it usually represents reactivation of rheumatic fever

Five Cases of Congenital Aneurysm of Aortic Sinuses (of Valsalva) and Notes on Prognosis Most recorded cases have been diagnosed at autopsy H Gosta Davidsen Jørgen Fabricius and Erik Hu feldt[6] (Univ of Copenhagen) present the clinical picture and special methods of confirming diagnosis Early recognition is important if surgical correction is to be attempted

Man 32 first knew of murmur at age 17 but had had no symptoms except slight dyspnea and a feeling of tightness in the chest when he carried heavy luggage The chest wall bulged moderately over the lower precordium A rough systolic murmur heard over the whole precordial area was very distinct in the 2d and 4th left intercostal spaces at the sternal border where it was combined with a loud diastolic murmur giving the impression of a continuous machinery murmur The ECG was normal Chest x ray showed a broad heart shadow prominent pulmonary artery and conus of right ventricle Catheter studies showed a left to right shunt at the atria and ventricles with normal pressure

At age 38 the apical impulse had become heaving a thrill was palpable and the murmur was machinery type rough and continuous X ray showed considerable increase in heart size Repeat catheterization was unchanged Thoracic aortography showed the right coronary sinus to be dilated and projecting into the heart shadow

Death may be caused by rupture compression of the bundle of His impaired aortic valvular function or bacterial endocarditis Rupture is the most common Among 17 recorded cases 10 patients had rupture into the right atrium and survived 1 hour to 3 years Prognosis seems to depend on size of rupture but in general is so poor that surgical repair should be attempted despite considerable operative risk Prognosis in uncomplicated cases is unknown Probably a number of patients go through life with little or no symp

(6) Acta med scand 160 455-470 1958

the anomalous artery at its origin from the pulmonary artery If the vessels supplied by the aberrant become visibly larger and the myocardium pinker the ligation should be *made permanent If these events do not occur* poor anastomoses between the two coronary arteries is suggested and an attempt should be made to create pulmonic stenosis Whether any surgical procedure will be of long term value remains in doubt because of the severity of myocardial damage in most patients

Postpericardiotomy Syndrome Following Surgery for Nonrheumatic Heart Disease Tomiko Ito Mary Allen Engle and Henry P Goldberg[5] (New York Hosp Cornell *Med Center) observed a condition indistinguishable from* the postcommissurotomy syndrome in 13 patients with congenital malformations of the heart who survived intrapericardial surgery It appeared as frequently (in 13 of 24 patients with pericardiotomies) as has been reported in rheumatic patients who recovered from mitral valve surgery (10-40%) The syndrome developed after transventricular and transarterial valvoplasty for pulmonary stenosis closure of septal defects and exploration of the pericardium for inoperable *congenital cardiac lesions*

All patients with the syndrome had fever in the immediate postoperative period In 11 fever recurred within 1 week to 1 month postoperatively and lasted 3 10 days All the adults and 2 children complained of chest pain during the febrile episode The pain frequently radiated posteriorly to the subscapular region and was often aggravated by breathing Two patients had a feeling of substernal constriction and 2 complained of difficulty in swallowing 10 had an associated nonproductive cough and 2 adults complained of generalized muscle aches and pains but there were no complaints of arthralgia or objective signs of arthritis The white blood cell count was usually in the range of 10 000/cu mm The pleural and pericardial effusions resolved spontaneously Antibiotics did not seem to influence the development or subsidence of the syndrome Hormone therapy was not used

The feature common to these operations in the nonrheumatic as well as the rheumatic patients was wide incision of the pericardium This postoperative complication was not noted after other *operations for congenital heart disease in*

(5) Circulation 17 549 556 April 1958

diate correction A possible exception to this generalization is the repair of ventricular diverticula that may be amen able to immediate correction

Some sternal defects will not require correction Minor ab normalities of the lower sternum are not cosmetically or physiologically serious If however the defect is extensive immediate repair must be strongly considered because the correction of large defects becomes progressively more dif ficult with advancing age

Marfan s Syndrome Associated with Pregnancy According to Howard A Novell Leo A Asher Jr and Maurice Lev[8] (Mt Sinai Hosp Miami Beach Fla) this syndrome which has a familial inheritance affects the skeleton and eyes and the pulmonary and cardiovascular systems The cardio vascular abnormality consists of inherent weakness in the media of the aorta and pulmonary artery leading to diffuse dilatation of the ascending aorta and/or pulmonary artery producing aneurysms of these vessels and often dissecting aneurysms in the aorta Congenital cystic disease of the lung is a frequent complication

The patient is tall and thin with little subcutaneous tissue which gives an aged and drawn expression The great toe is markedly enlarged compared with the other toes The face is long and narrow the palate high and arched and there is a tendency to prognathism Excessive longitudinal growth of the ribs may lead to pectus excavatum or pigeon breast The joint capsules fasciae and ligaments are redundant and weak The commonest abnormality of the eye is ectopia lentis or subluxation of the lens The sclera may be blue or cloudy

Because of the poor prognosis for life in pregnant women with Marfan s syndrome the obstetrician should be on the alert for the diagnosis when a patient presents with the clini cal stigmas of the disease A complete cardiovascular and pulmonary evaluation including angiocardiography should be made If aneurysm is demonstrated the patient should be advised of the prognosis Therapeutic abortion and subse quent sterilization should be considered depending on whether the patient wishes to take the risk of rupture or dissection during pregnancy *No cure is known*

(8) Am. J Ob t & Gy c 75 80 812 Ap 1 1958

toms until death from other causes Surgery is inadvisable in uncomplicated cases without marked symptoms

Indications for surgical repair are rupture into the right atrium provided considerable left to right shunt into the right atrium is present there are no signs of a complicating interventricular septal defect and there is no endocarditis syphilis or arteriosclerosis Detailed diagnostic study is indicated in patients with sudden precordial pain dyspnea and signs of rapidly increasing cardiac failure if examination reveals a loud systolic diastolic or continuous machinery murmur located near the lower end of the sternum A high pulse amplitude and a pistol shot sound over the femoral artery are usually present

Syndrome of Congenital Defects Involving Abdominal Wall Sternum Diaphragm Pericardium and Heart was studied by James R Cantrell J Alex Haller and Mark M Ravitch[7] (Johns Hopkins Univ) in 21 patients This complex should be considered as a specific syndrome It is inadequate and inaccurate to consider such patients as having ectopia cordis The entire group of anomalies appear closely related in embryologic development arising as the result of defective formation and differentiation of the ventral mesoderm at about 14 18 days of embryonic life The unusual ventral defect of the diaphragm noted in these patients results from failure of the transverse septum to develop This specific anomaly has failed to gain proper recognition in the classification of congenital diaphragmatic defects The consistent association of congenital intracardiac lesions has not been previously noted An interventricular septal defect is invariably present Co existence of serious unrelated anomalies is rare

In view of the multiplicity of problems posed by these patients it is not practical to formulate a specific plan of attack that will be optimal for all but in general treatment should consist of immediate surgical correction of as many of the defects as possible Repair of the cardiac lesions should be deferred because diagnosis in the neonatal period is difficult and inexact Total correction will require an open heart procedure in most or all of these patients and this technic is unsatisfactory in the newborn The cardiac lesions noted in the study patients were not so severe as to require imme

(7) Surg Gynec & Obst 107 602 614 November 1958

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(8) Am J Ob t & Gy 75 80 81 April 1958

RHEUMATIC AND VALVULAR HEART DISEASE

Differential Diagnosis of Rheumatic Fever still may present considerable difficulties particularly in its milder forms Some of these difficulties are insurmountable Others could be overcome by more rigid adherence to diagnostic criteria more critical examination of the problems presented and increased awareness of the significance of the physical signs elicited

K A Hallidie Smith and E G L Bywaters[9] (Canadian Red Cross Mem l Hosp Taplow) reviewed the records of 160 of 959 patients discharged with the diagnosis of rheumatic fever between July 1947 and June 1956 All were children aged 6 12 who were regularly followed after discharge for 18 months to 7 years In 12 the original diagnoses had been poliomyelitis pneumonia meningitis rubella dysentery subacute bacterial endocarditis appendicitis suppurative arthritis of hip Still s disease and fallen arches

During this 9 year period 196 patients were admitted with the presumed diagnosis of rheumatic fever but diagnosis was not substantiated in follow up varying from none in a small minority to several years in some No rheumatic activity was evident at these check ups and no patient acquired organic heart disease during the period of observation The final diagnoses were functional murmurs traumatic and postural joint disorders infections connective tissue disorders rheumatic and congenital heart disease (not rheumatic fever) blood dyscrasias and other joint involvement

The early acute stage of rheumatoid arthritis closely resembles rheumatic fever especially in children with pericarditis salicylate responding pyrexia and transient joint involvement The Rose Waaler test is usually negative Only continued observation of the subsequent course of the disease or development of endocarditis erythema marginatum or chorea provides a solution

A careful history is essential in exclusion or confirmation of the less typical forms of acute rheumatism Temperatures of 98 8 99 4 F have often been cited as being a significant

(9) A ch D Childhood 33 330 357 Augu t 1958

feature but an isolated finding in a child This is probably of little consequence since a normal child s temperature may often reach these levels at some time in the 24 hours Tachycardia has also often been erroneously stressed Even mild apprehension can cause tachycardia in a nervous child but the sleeping pulse will be within normal range for the age group A systolic murmur which may be innocent is found in many infants and most normal children and is thought to be related to flow of blood in the great vessels It is accentuated in the febrile child whose cardiac output is increased Such a murmur is usually maximal in early or midsystole low pitched and musical or high pitched and blowing In contrast the organic systolic murmur is smooth and high pitched fills systole is best heard at or just internal to the apex and is propagated toward the axilla The sedimentation rate is of particular value in differential diagnosis since a normal rate (less than 15 mm /hour Westergren) at onset of disease makes the diagnosis of active acute rheumatism unlikely

Diagnosis and Treatment of Rheumatic Fever and Rheumatic Carditis Benedict F Massell[1] (Harvard Med School) studied 457 initial attacks of rheumatic fever in patients under age 17 Significant cardiac murmurs were found in 53% of the patients These were due to mitral regurgitation alone in 71% mitral and aortic regurgitation in 22% and aortic regurgitation alone in 7%

Incidence of definite pericarditis with rheumatic valvular involvement was about 12% Incidence of congestive heart failure was 7 9% Prolonged P R interval was seen in 25% Incidence of subcutaneous nodules was 12% Multiple nodules were usually accompanied by rheumatic valvular involvement Multiple nodules without cardiac involvement indicate rheumatoid arthritis or some other collagen disease but when accompanied by rheumatic heart disease the patient almost certainly also has active rheumatic fever rather than bacterial endocarditis or some other complicating disease Erythema marginatum occurred in 11% of the patients

Incidence of chorea when associated with significant murmurs or other stigmas of rheumatic fever was 13% Fever was observed in 89, and elevation of the sedimentation

(1) M Cl N rth Am r 4 1343 1360 S p be 1958

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Differential Diagnosis of Rheumatic Fever still may present considerable difficulties particularly in its milder forms Some of these difficulties are insurmountable Others could be overcome by more rigid adherence to diagnostic criteria more critical examination of the problems presented and increased awareness of the significance of the physical signs elicited

K A Hallidie Smith and E G L Bywaters[9] (Canadian Red Cross Mem l Hosp Taplow) reviewed the records of 160 of 959 patients discharged with the diagnosis of rheumatic fever between July 1947 and June 1956 All were children aged 6 12 who were regularly followed after discharge for 18 months to 7 years In 12 the original diagnoses had been poliomyelitis pneumonia meningitis rubella dysentery subacute bacterial endocarditis appendicitis suppurative arthritis of hip Still s disease and fallen arches

During this 9 year period 196 patients were admitted with the presumed diagnosis of rheumatic fever but diagnosis was not substantiated in follow up varying from none in a small minority to several years in some No rheumatic activity was evident at these check ups and no patient acquired organic heart disease during the period of observation The final diagnoses were functional murmurs traumatic and postural joint disorders infections connective tissue disorders rheumatic and congenital heart disease (not rheumatic fever) blood dyscrasias and other joint involvement

The early acute stage of rheumatoid arthritis closely resembles rheumatic fever especially in children with pericarditis salicylate responding pyrexia and transient joint involvement The Rose Waaler test is usually negative Only continued observation of the subsequent course of the disease or development of endocarditis erythema marginatum or chorea provides a solution

A careful history is essential in exclusion or confirmation of the less typical forms of acute rheumatism Temperatures of 98 8 99 4 F have often been cited as being a significant

(9) A ch D s Ch ldhood 33 3!

ficiency and tricuspid insufficiency Dusky nail beds and extremities were often observed especially during severe heart failure

A tricuspid diastolic thrill and murmur were detected in 11 patients both usually in the 3d 4th or 5th intercostal space between the left sternal border and nipple line The 5th intercostal space parasternally was the commonest site of maximal intensity The murmur was early and middiastolic when associated with atrial fibrillation and diastolic presystolic with normal sinus rhythm It was low pitched coarse and rumbling and was heard better with the bell stethoscope attachment Stepwise auscultation from the apex to the tricuspid area helped separate the tricuspid diastolic murmur from the mitral diastolic murmur A small relatively silent area could usually be found between the two valve areas The murmur of tricuspid stenosis and if present that of tricuspid insufficiency always increased in intensity during inspiration and decreased during expiration Conversely the murmurs at the mitral area faded during inspiration and became more intense during expiration

X rays showed enlargement of the right atrium in each patient noted best in the frontal and right oblique views In 3 patients the atria were gigantic and displaced the right border far into the lung The angiocardiogram showed characteristic right atrial enlargement and opacification The ECG s in patients with normal sinus rhythm showed sharply peaked P waves of increased amplitude most striking in leads II V_1 and V Bifid P waves of increased duration were present in 5 of the 7 patients with combined mitral and tricuspid stenosis

With these criteria diagnosis of tricuspid stenosis is possible in a high percentage of cases If the lesion is suspected right heart catheterization with studies at rest and exercise is the most useful procedure for confirming diagnosis The drop in pressure across the valve during diastole may be only a few millimeters of mercury Uncorrected tricuspid stenosis may obscure the beneficial effect of successful mitral valvuloplasty and may be the cause of persistent disability

Tricuspid Regurgitation Masquerading as Mitral Regurgitation in Patients with Pure Mitral Stenosis Tricuspid insufficiency arises in patients with chronic rheumatic heart

rate in 92% One or the other or both manifestations were noted in 97% Except in pure chorea some fever is usually present at onset of rheumatic fever In initial attacks of rheumatic fever antistreptolysin O titers of 400 units or more were recorded in 82% Joint pain occurred in 90% of the 457 initial attacks

Early diagnosis often depends on recognition of a syndrome consisting of joint pain fever and/or elevation of the sedimentation rate and elevation of the antistreptolysin O titer Among the author s patients this syndrome occurred in 74%

Of 304 patients with an initial attack of rheumatic fever who did not have pure chorea and who received little or no antirheumatic therapy in almost 80% all evidence of active rheumatic fever had subsided within 12 weeks and in almost 90% within 15 weeks Thus in most the initial attacks were self limited

Treatment of acute rheumatic fever should include penicillin first in therapeutic then in prophylactic doses and aspirin or adrenocortical steroids

Tricuspid Stenosis Clinical Features in 12 Cases are reported by Thomas Killip III and Daniel S Lukas (New York Hosp Cornell Med Center) The 12 patients were aged 23 52 11 were women Five had had polyarthritis or chorea in childhood and in 9 murmurs had been noted before age 16 Symptoms were variable Each had had dyspnea on exertion This was a major symptom in 1 and was relieved by mitral valvuloplasty In 8 orthopnea and chronic fluid retention were pronounced Chronic edema requiring mercurial diuretic therapy occurred in every patient with atrial fibrillation Severe fatigue observed in 10 patients was prominent in 5

Pulmonary edema was evident in 7 patients with severe right heart failure and associated pulmonary symptom Hepatomegaly was seen in all but 3 The largest livers were found in patients with atrial fibrillation plus tricuspid insufficiency and stenosis Among 6 with normal sinus rhythm distinct presystolic pulsations of the liver were noted in 3 Prominent presystolic pulsations of the external jugular veins were seen in 4 Systolic pulsations of the liver and external jugular veins were present in all 6 with atrial insuf

(2) Am J M d 4 816 85 J e 1958

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disease when leaflet tissue is destroyed or the right ventricle dilates Persistent right sided heart failure accompanied by pulsating neck veins and liver should suggest the diagnosis X ray evidence of right atrial enlargement and ventricular contour of the right atrial pressure waves at catheterization should partially confirm the diagnosis

The lesion is accompanied by a systolic murmur usually heard best at the lower sternum or 4th left interspace However it may be obscured by associated valve defects which dominate the clinical findings or be erroneously attributed to a nonexistent lesion In marked right ventricular hypertrophy with clockwise rotation of the heart in patients with tricuspid insufficiency and mitral stenosis the tricuspid murmur may extend toward the apex and may be mistaken for mitral insufficiency This is a significant error in patients being evaluated for mitral commissurotomy

Joseph F Uricchio Lamberto Bentivoglio Richard Gilman and William Likoff[3] (Hahnemann Med College) studied 5 patients in whom the clinical features of pure mitral stenosis and tricuspid regurgitation masqueraded as mitral regurgitation All had marked fatigability and exertional dyspnea orthopnea or paroxysmal nocturnal dyspnea and engorged neck veins which pulsated in 4 The liver was enlarged in all but pulsated in only 2 Auscultatory evidence of mitral stenosis was unequivocal sharp 1st sound and mid late diastolic rumble Each patient had a loud rather harsh systolic murmur at the apex with maximal intensity at the lower left sternal border and at the xiphoid transmitted mainly toward the axilla or base of the heart and unaltered by exercise inspiration or change in position In each the ECG showed right ventricular hypertrophy X rays showed increased size of the right atrium and ventricle in each but only moderate enlargement of the left atrium Left heart catheterization revealed marked elevation of the left atrioventricular gradient filling pressure in 4 Ventriculography revealed reflux of dye across the tricuspid orifice in each patient in whom this was performed but not across the mitral valve in 1 patient in whom this was tested Surgical exploration confirmed marked mitral stenosis and tricuspid insufficiency in all patients

Correct diagnosis depends on careful evaluation of sub

(3) Am J M d 25 4 230 A g t 1958

jective and objective findings The most direct way to establish the diagnosis of tricuspid insufficiency involves opacification of the right or left ventricular chamber by ventriculography Rapid injection of Diodrast® into the left ventricle in these patients fails to demonstrate regurgitation across the mitral valve and opacification of the left atrium Injection into the right ventricle however reveals regurgitation into the right atrium

► [Patients with mitral stenosis commonly have systolic murmurs due to four different causes The bruit of mitral insufficiency is usually loudest at the apex and frequently radiates toward the axilla but may be well heard at the aortic area However a thrill in the latter region constitutes strong evidence that the murmur in the right 2d interspace is due to stenosis of the aortic valve The features of the murmur of tricuspid insufficiency are well described in this and the following report The commonest systolic murmur however in patients with mitral stenosis is an ejection murmur in the pulmonary area This is apparently related to the increased pressure and perhaps the dilatation of the pulmonary artery

The differentiation of these four common causes of systolic murmurs is of great practical significance because the presence of a well marked mitral insufficiency or of aortic stenosis increases the operative hazard and reduces the likelihood of a successful result from mitral commissurotomy On the other hand neither the murmur of tricuspid insufficiency nor the common murmur in the pulmonary area constitutes a contraindication for operation on the mitral valve —Ed]

Clinical Study of 111 Cases of Tricuspid Insufficiency is reported by J Himbert J Joly and J Lenegre[4] Clinical diagnosis was established in 105 by an enlarged liver stimulated by definite systolic expansion In 6 systolic expansion was absent but hemodynamic studies revealed a significant right auricular reflux The patients were aged 12 72 (average 40 8) 57 were aged 30 50 and 61 were female In all cases tricuspid insufficiency was associated with other heart disease In 86 (77 4%) this was of rheumatic type in 9 arterial in 9 due to a chronic pulmonary lesion and in 7 due to other cardiac lesions All patients had clinical examination 91 were studied radioscopically and radiographically 97 had complete ECG s and venous pressure was measured in 97

Cardiac symptoms were dominated clinically by a xyphoid systolic murmur (50%) and Carvallo s sign (25%) X rays showed that the heart was enlarged in all patients with right reflux and a round point in 50% the more significant since lungs were clear Cardinal signs in the ECG were frequency of auricular fibrillation (66%) and evidence of right or bilateral ventricular hypertrophy In lead VI the initial

(4) S m h p P 34 194 214 M 18 1958

negativity of the QRS was observed in 25% of the patients and an incomplete right block in 22%

Systolic expansion of the liver and pain was found in 95% Venous pressure averaged 21 cm water Jugular veins were pulsating or systolic in almost 25% Edema (68%) and ascites (25%) were frequent Dyspnea was common (80%) but dependent on various mechanisms (chronic bronchopathy cardiac lung with continuous secondary pleural effusion pulmonary embolism compressive ascites and anoxia) The course was variable suggesting an organic basis for tricuspid insufficiency in almost 20% of the cases Forty three patients lived less than 3 weeks and 22 lived 3 weeks to 1 year The others lived 1 7 years

In terms of this critical study signs of tricuspid insufficiency may be grouped in two categories certain and presumptive Certain signs are those that furnish direct evidence of right auricular and venous regurgitation In order of frequency these are (1) systolic expansion of the liver (2) jugular venous pulse (3) xyphoid systolic murmur increasing definitely in postinspiratory apnea (Carvallo s sign) and (4) radiographic signs of transtricuspid reflux (systolic expansion of the right auricle and systolic raising of the right half of the diaphragm) Presumptive signs are not essentially different from signs of causal or associated cardiopathy or right cardiac insufficiency They are inconstant have value only when combined and are of two types Type I includes those that indicate major hypertrophy dilatation of the right cavities of the heart e g symptoms in the right axilla significant increase in cardiac size (by x ray) with right reflux and biventricular or right ventricular hypertrophy with incomplete right block or QR image in lead VI or auricular fibrillation or an isolated or predominant right auricular hypertrophy (by ECG) Type 2 includes those related to hemodynamics of tricuspid insufficiency which tend essentially to produce severe and permanent venous hypertension (significance of hepatomegaly frequency of cardiac cirrhosis and ascites) and to spare the pulmonary circulation (relative clearness of pulmonary fields and progression always poor in pleuropulmonary signs)

Method for Detection and Estimation of Aortic Regurgitant Flow in Man In the absence of aortic regurgitation ret

rograde blood flow in the aortic arch is minimal With aortic regurgitation however reverse flow in the aortic arch is increased and the volume of the retrograde arterial flow in excess of that which occurs normally is the volume of blood which regurgitates An estimate of the magnitude of aortic regurgitation may be obtained by injecting an indicator dye into the descending aorta and detecting its presence upstream

Eugene Braunwald and Andrew G Morrow[5] (Nat l Inst of Health) studied 26 patients by this method An indicator dye was injected at various levels in the descending aorta through a catheter introduced percutaneously from the femoral artery The lowest point in the descending aorta from which the injected dye regurgitated to the ascending aorta and perfused the right ear was determined by means of an oximeter placed on the right ear The volume of blood contained within the segment of aorta between this point and the detection site during diastole represents the volume of reversed aortic flow this in turn is a function of aortic regurgitant flow

No complications from the catheterization occurred The 7 patients used as controls had neither clinical nor hemodynamic findings suggestive of aortic regurgitation Dye injected into the aorta immediately distal to the aortic arch could not be detected in the right ear during its primary circulation in any of these patients In all 10 patients in whom there was firm clinical evidence of aortic regurgitation dye injected into the descending aorta could be detected in the right ear

This procedure was of particular value in the assessment of patients with an equivocal diagnosis of aortic insufficiency among whom were those with high pitched decrescendo diastolic murmurs at the left sternal border The exclusion of aortic regurgitation by this technic may help to establish more definitely the incidence of pulmonic incompetency as well as the clinical and hemodynamic picture with which this lesion is associated

Significant aortic regurgitation was detected in a patient without the characteristic murmur and in another whose predominant lesion was subvalvular aortic stenosis In patients with left to right shunts originating from the aortic

(5) Circulation 17 05 511 Ap 1 1958

root blood also regurgitates into the ascending aorta during diastole and the authors technic permits estimation of the diastolic component of the shunt Differential diagnosis between such a shunt and aortic insufficiency can be made by injection of the dye into the ascending aorta and observance of the contour of the dilution curve obtained from the femoral artery

The method proved of value in assessing the magnitude of regurgitation in patients with mixed aortic valve lesions being selected for aortic commissurotomy It also furnishes an index of the effect of operation on the aortic regurgitant flow Although the technic cannot directly measure aortic regurgitation before and after the insertion of a *Hufnagel* valve it should prove useful in assessing the effectiveness of prostheses placed into the ascending aorta or left ventricle

Clinical and Instrumental Evaluation of Associated Mitral and Aortic Stenosis in 30 patients (21 females) mostly of rheumatic origin is presented by G Gamna L Dughera C Quaglia and E Jona[6] (Univ of Turin) Associated mitral and aortic defects occurred in about 30% of all undergoing complete cardiac study Exact clinical definition of preponderance of the mitral and aortic defect or their equivalence is important in planning appropriate surgical treatment On this basis the authors divided the patients into three principal groups

In group 1 comprising almost half the patients mitral stenosis prevailed over the aortic Subjective symptoms were typical of right insufficiency stethoacoustic signs of mitral stenosis were always evident but there was a slight systolic murmur in the aortic area which was too feeble to be transmitted to the cervical vessels and which in the phonocardiogram resulted in vibrations of low amplitude and average frequency with mesosystolic augmentation In these patients phonocardiograms by the esophageal route were particularly useful with registration on the right and left sides by means of the moving bed technics that make the systolic murmur more evident In the ECG right preponderance prevailed with right axial deviation and often a right ventricular surcharge Appearance of the QRS complex in left precordial leads should be analyzed carefully to discover the first signs of left ventricular hypertrophy More signifi

(6) P sse m d 66 1693 1696 Oct 29 1958

cantly though also slight were the left ventricular hyper trophy and moderate dilatation of the ascending aorta ob servable in routine x rays in these cases angiocardiography was important besides revealing the mitral stenosis it in dicated more exactly the thickne s of the left ventricular wall dilatation of the ascending aorta with a right half moon profile along with greatly retarded evacuation of the left ventricle and aorta Analytic kymography (Cignolini) may reveal early aortic stenosis Sphygmographic examina tions indicated an increase in periods of typical tension of mitral stenosis and also a slight increase in emptying time which may furnish important orientation

In group 2 representing about one fourth of the series he modynamic effects of the two defects were practically equal In this situation it is often possible (4 cases) to obtain prac tically normal FCG and x ray findings The right chamber of the heart and the left auricle were slightly enlarged and the left ventricle was moderately increased an appearance *better shown by angiography (thickness of the wall mod* erate aortic dilatation) Phonocardiography showed in ad dition to signs of mitral stenosis moderately intense systolic vibrations tending to form a diamond Systolic blow may be irradiated toward the neck vessels but a basal systolic mur mur was never observed The ECG may be normal and the electric axis is often in equilibrium in only 2 cases was there a concomitant left ventricular hypertrophy Analytic kymog raphy showed signs of aortic stenosis uninfluenced by the presence of mitral stenosis and sphygmography a moderate increase in emptying time

In group 3 representing about 20% of the patients aortic stenosis predominated Subjectively anginal pain at rest and after effort and lipothymia were typical but not always present In some but not all of these patients basal systolic murmur could be heard On auscultation the systolic blow ing murmur typical of closed aortic steno is was transmit ted to the jugular vein and vessels of the neck and in the pho nocardiogram was diamond shaped The importance of the aortic factor should not lead to underestimation of the mitral stenosis because acoustic signs of the latter are often not very evident The ECG is of pathognomonic importance when besides signs of striking left ventricular hypertrophy there is a tendency toward right deviation of the electric axis

or of atrial fibrillation Simple x rays show slight signs of pulmonary stasis moderate increase of the right cardiac chambers and of the left auricle whereas general configuration of the heart has the typical aspect on filling Angiocardiography reveals all the signs of left ventricular hypertrophy with an ectatic venous tree and slightly altered arterial system Venous return is prolonged to 14 16 seconds Intensity of left ventricular opacity is often marked with tonalities of shadow which contrast with the slightly injected aorta There is less retardation in emptying of the left ventricle (to 16 seconds) compared with patients who have predominant mitral stenosis Analytic kymography showed definite signs of aortic stenosis The sphygmogram showed greatly increased emptying time (isotonic systole) even though the values seen in pure aortic stenosis were not reached

Controlled mitral commissurotomy can be performed in mitral stenosis associated with mild aortic stenosis or insufficiency but this operation may be contraindicated with severe aortic insufficiency although the present trend is toward simultaneous surgical attack on both constricted valves

Lung Compliance in Patients with Mitral Stenosis According to H C White J Butler and K W Donald[7] (Birmingham England) increased fluctuations of intrapleural pressure occur on respiration in patients with heart disease particularly in those with cardiac failure These wide pressure changes are necessary in part to overcome an increase in the resistance of the lungs to deformation

The low compliance has been correlated with a reduction in vital capacity and with changes in the structure and hemodynamics of the lungs and pulmonary vascular bed In acute animal experiments clamping the pulmonary vein results in reduced lung compliance and vital capacity the change in vital capacity being irreversible if pulmonary edema occurs

Presumably an ill defined state of pulmonary congestion is responsible for the changes in divisions of lung volume and in pulmonary distensibility Pulmonary congestion may be interpreted as an increase in pulmonary vascular pressures an increase in the amount of blood or transudate in the lungs or a combination However no increase in in

(7) Cl n S 17 667 679 Novembe 1958

trathoracic blood volume has been found in mitral stenosis although lung compliance in patients with this condition tends to be reduced

The relation between hemodynamic changes and lung compliance is still in considerable doubt The authors investigated this relation in patients with mitral valve disease by measuring lung compliance pulmonary vascular pres ures and blood flow simultaneously both at rest and on exercise The mean lung compliance at rest was 0 12 L /cm H O which is significantly lower than normal Compliance was lowest in the most disabled patients Compliance at rest was normal in patients with normal pulmonary wedge pressures In patients with wedge pressures even slightly above normal compliance was usually reduced Compliance fell markedly as wedge pressures and pulmonary arterial pressures rose on exercise and distention pressure wa directly related to pulmonary vascular resistance on exercise

The fall in compliance on exercise in these cardiac patients may be mainly dependent directly on acute hemodynamic changes and not secondary structural changes such as may account for the low resting compliance

Role of Vessel Tone in Maintaining Pulmonary Vascular Resistance in Patients with Mitral Stenosis was studied by Herbert J Semler John T Shepherd and Earl H Wood[8] (Mayo Clinic and Found) Patients with mitral stenosis have medial hypertrophy of the pulmonary arteries and a muscular media in the arterioles These changes often are accompanied by an increased resistance to blood flow through the lung vessels Many attempts have been made to define the mechanism of this increased resistance with the use of adrenergic and ganglion blocking agents The conflicting nature of the conclusions is mainly due to the fact that the potent action of these drugs on the systemic circulation makes it difficult to decide whether the changes in the pulmonary circulation are actively or passively induced The recent use of acetylcholine injected into the pulmonary artery in such concentration that it is inactivated before reaching the left side of the heart has demonstrated that the high pulmonary vascular resistance in mitral stenosis is at least partly functional that is tone is present in the smooth muscle of the

(8) C l t n 19 386 394 Ma h 1959

pulmonary vessels and this contributes to the pulmonary hypertension

The authors measured the pulmonary vascular (arteriolar) resistance in 58 patients with predominant mitral stenosis during exercise and 2 5 weeks and 8 30 months after mitral valvotomy Mitral valvotomy resulted in decreased resistance that was directly proportional to the magnitude of resistance before operation Many patients showed an increase in resistance during exercise and especially those with a mean pulmonary artery pressure on resting in excess of 30 mm Hg

These changes in resistance appear to represent active changes in the caliber of the pulmonary vessels due to alteration in their smooth muscle tone with valvotomy causing a decrease in tone and exercise causing an increase in tone

Recent studies on the human systemic circulation have shown the importance of changes in transmural pressure in modifying vessel tone The authors findings suggest that changes in pressure somewhere in the pulmonary vascular bed or the left atrium may be a stimulus capable of regulating tone in the pulmonary vessels

These alterations in tone could be affected either through a local nonnervous response of the smooth muscle to the changes in pressure such as has been described for the systemic vessels or to local nervous reflexes from the increase in pulmonary venous or left atrial pressure

Six Years Experience with Mitral Commissurotomy during Pregnancy is reported by G Leslie Watt W G Bigelow and W F Greenwood[9] (Toronto Gen l Hosp) The series of patients included 24 operated on between months 2 and 6½ of pregnancy All belonged to classes III and IV of the New York Heart Association functional classification Selection of patients was made purely on a basis of heart disease and the operation was performed at the stage of pregnancy when the indications occurred Average age was 30 years None of the patients died after operation and none had any sign or symptom of threatened abortion From the time of operation to delivery only 1 patient did not improve At birth only 1 baby was difficult to resuscitate and there was only 1 whose delivery was described as precipitate

On the basis of their experience the authors believe that

(9) Am J Ob t & Gyn 77 507 512 M h 1959

a pregnant mitral stenosis patient with a history of failure in a previous pregnancy or a patient with failure in the pres ent pregnancy should undergo mitral commissurotomy as soon as possible The operation may be done safely as long as there is time for recovery from the operation before the peak load of pregnancy is reached which would mean not later than 6½ months except in some most unusual cir cumstances Heart failure characterized by pulmonary edema should be regarded as an absolute indication for op eration which should be carried out as soon as possible Each case must be considered on its own merits and the deci sion made purely on the basis of heart disease after the most careful assessment by a cardiologist If this is done preg nancy does not seem to add to the hazard and the results will surely justify the procedure

Therapeutic abortion should be reserved for those patients who cannot qualify for the operation or who refuse it and whom it is thought unwise to carry through pregnancy with medical treatment Sterilization after the operation seems to be indicated only in cases in which the result has been disappointing and the usual cardiac reserve has not re turned Further pregnancies in the patient who has done well may be looked forward to without fear

Surgical Treatment of Acquired Valvular Disease is reviewed by Dwight I Harken[1] Patients with mitral stenosis are divided as follows group I no disability group II mild nonprogressive limitation group III pure mitral stenosis and progressive symptoms with compensation disintegrat ing and group IV terminal phases generally with refrac tory congestive failure

Surgical mortality has fallen dramatically Group III pa tients have a 0 6% mortality a level comparable to other gen eral surgical procedures The mortality in group IV patients remains high (20%) Atrial fibrillation is not a contraindica tion to surgery Preoperative reversion to normal sinus rhythm is ill advised because fibrillation often starts again after surgery

Valvuloplasty significantly reduces danger of embolism in mitral stenosis presumably because stasis is reduced and the appendage is removed Repeated emboli within a few weeks

(1) C culat n 18 1 6 J ly 1958

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Successful Treatment with Vancomycin of Septicemia Following Mitral Commissurotomy Caused by Antibiotic Resistant Strain of Staphylococcus Aureus is described by S Stanley Schneierson Eugene L Komrad and Morton S Bryer Mortality from Staph aureus septicemia closely parallels that existing in the preantibiotic era Although many factors including innate host immunity and concomitant or underlying disease e g malignancy etc undoubtedly exert considerable influence in each patient development of resistance by staphylococci to once effective antimicrobial agents has played an important role in this situation

Vancomycin a new antibiotic isolated from strains of Streptomyces orientalis has been reported to have several favorable properties Among these are low toxicity bactericidal activity in low concentrations against gram positive micro organisms including many strains of staphylococci resistant to current antibiotic agents as well as minimal development of experimentally induced resistance after repeated subculture in graded concentrations of the drug Vancomycin readily protects laboratory animals against experimental infection with staphylococci streptococci and pneumococci

In a woman aged [illegible]6 Staph aureus sepsis developed after valvulotomy for correction of mitral stenosis A few days after surgery bacterial endocarditis suppurative pneumonia and vascular collapse developed The causative organism was resistant to penicillin streptomycin and erythromycin but was sensitive to vancomycin The patient was started on hydrocortisone 100 mg intravenously daily and on antibiotics consisting of 4 Gm vancomycin 10 000 000 units of penicillin intravenously and 1 Gm streptomycin intramuscularly daily The temperature and white blood count dropped abruptly Blood cultures taken after the 3d day of introduction of vancomycin therapy revealed no growth The patient had uncomplicated convalescence since the 1st week after vancomycin therapy The progressive normochromic normocytic anemia that developed during vancomycin treatment was believed due to toxic metabolic reaction rather than to any specific hemopoietic depression by vancomycin

Familial Pseudoxanthoma Elasticum and Valvular Heart Disease Jay D Coffman and Sheldon C Sommers[3] (Boston Univ) observed a patient with pseudoxanthoma elasticum who died in congestive heart failure due to mitral stenosis

Woman 68 was hospitalized because of shortness of breath Past history revealed influenza but no other episodes suggestive of rheumatic fever The patient was obese and dyspneic. The heart was enlarged Its first sound was accentuated and an opening snap was

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may constitute an urgent indication for valvuloplasty Danger of emboli at surgery is reduced by flushing the atrium to evacuate thrombi from the appendage occluding the cervical vessels after fracturing through calcific areas in the valve and fracturing through areas of the valve less likely to mobilize calcific fragments Failure to obtain good valvuloplasty initially is the commonest cause for poor surgical results Reoperation must be considered when any patient with pure mitral stenosis fails to show or maintain improvement Some clinicians consider patients past 50 too old for valvuloplasty However the author has successfully operated on about 200 aged 50 70

Aortic stenosis can be partially corrected by direct digital manipulation with use of a valvulotome if necessary through a tunnel in the side of the aorta base Open technic is not required The mortality rate steadily decreased until among the last 40 patients only 2 died an operative mortality of only 5% Of 52 patients with aortic stenosis who did not have surgery 47 died within 6 months after surgery had been advised

Left ventricular failure manifested by progressive dyspnea despite adequate medical therapy is an urgent indication for aortic valve operation Even when left heart catheterization is unimpressive clinical palliation may be excellent Aortic and mitral stenosis can be corrected at the same operation if necessary Preoperative determination of valve gradients cardiac output and dye dilution curves is necessary Surgical correction of tricuspid stenosis is technically easy but rarely indicated In aortic insufficiency surgery is incomplete and only palliative which makes recognition of the role of surgery the more difficult There are minor hemodynamic problems that are handled better by waiting for more advanced operative procedures Rigid medical treatment may be life saving

Severe mitral valve regurgitation will be better treated by more definitive operation in the future The simplest operation now available for severe pure mitral regurgitation appears to be mitral circumclusion but the most definitive therapy is by open operation Mild regurgitation may be improved by compressing the annulus at the atrioventricular groove with compressed Gelfoam®

smooth margin are oval elliptical or fissure like and their long axis i at right angles to the free margin of the valve They are also generally bounded by the fibrous bundles of the valves so that the atrophy at least at first attacks only the thinnest portions Besides considerable and appre ciable attenuation of the valve and in some cases even per foration we occasionally find some portions as for instance the free margin the nodule and the fibrous bundles passing from it thickened and hypertrophied

Among the 342 hearts examined 247 (72%) showed some fenestration The aortic valve was affected slightly oftener than the pulmonic but each valve was involved in more than half the cases The two valves were affected together about twice as often as they were independently In more than a third only a single cusp was affected The left anterior aortic leaflet showed the highest and the anterior pulmonic cusp the lowest incidence of fenestration

Incidence and severity of fenestration were about the same for Negro and white races but were considerably higher in men than women In general older age groups showed a higher incidence of fenestration Even in the first decade of life 13 of 20 hearts (65%) had demonstrable fenestrations in the semilunar valves In children the openings were tiny sometimes only 1 or 2 isolated pinhead sized holes In older persons they were enlarged both in number and area

In patients with systemic or pulmonic hypertension the increased incidence of fenestration affected both semilunar valves but was greater in the leaflet under stress With wid ening of either valve ring severity and frequency of fenes tration increased in both semilunar valves

The exact cause of the lesion is not clear The authors be lieve that it may be a form of atrophy which may begin in early childhood or even in the fetus and that aging dilata tion of the ring and increased intravascular pressure are con tributing and modifying factors

Most fenestrations of the semilunar cusps are clinically un important Occasionally they give rise to diastolic murmurs which are confused with murmurs of organic valve disease When hypertension aortic dilatation and chest pain are pres ent as they often are the picture may mimic dissecting aneu rysm Functional diastolic murmurs of the aortic and pul

heard A grade 2 low pitched rumbling middiastolic murmur was localized to the apex A grade 3 rough blowing systolic murmur was loudest at the apex and radiated to the axilla Chest x rays showed a markedly enlarged heart with a contour suggesting pericardial effusion An ECG revealed atrial fibrillation The morning after admission the patient suddenly became very dyspneic vomited a small amount of material and died

At autopsy the endocardium of the left atrium was thickened and whitish yellow The mitral valve had a hard rolled ridge along the closure line and was definitely stenotic Microscopic studies revealed far advanced degeneration of the elastic fibers in the endocardium. Lack of vascularization of the valves the normal chordae tendineae and absence of Aschoff bodies ruled against the diagnosis of inactive rheumatic heart disease The patient had shown no obvious skin changes except the subcutaneous hemorrhages also described in pseudoxanthoma elasticum The skin blood vessel and kidney sections showed the changes of pseudoxanthoma elasticum

Inheritance of pseudoxanthoma elasticum is usually as an autosomal recessive but rarely is it transmitted as a dominant Parental consanguinity is common in the latter case Microscopic study of the skin from 5 of the patient s 6 children revealed changes consistent with pseudoxanthoma elasticum The patient and her husband were of different racial backgrounds and a skin biopsy from the husband failed to reveal evidence of pseudoxanthoma elasticum

When a patient with valvular heart disease lacks a history of rheumatic fever pseudoxanthoma elasticum should be considered

Fenestration of Semilunar Cusps and Functional Aortic and Pulmonic Valve Insufficiency Ben Friedman (Southwestern Med School) and Beulah M Hathaway[4] (Univ of Alabama) report 2 cases and review the appearance of the semilunar valves in 342 autopsies

Rokitansky who first adequately described the pathology stated The perforations are almost always near the free margin of the valves and more especially near their insertion where they originate increasing in numbers as they spread toward the nodules of the valve They are at first about the size of a pinhole or of a poppy seed but by confluence they finally attain the size of a grain of millet or of a hempseed or even of a pea When several are present together they impart a reticular broken appearance to the valve The perforations are moreover surrounded by a

(4) Am J Med 24 549 558 Apr 1958

atheromas in 50% of the coronaries Korean and Chinese soldiers eating no milk products and few eggs or meat fat had no lipid in the coronary intimas

Today thrombosis dominates much of the thinking about coronary disease Some investigators emphasize the role of heredity or of socioeconomic stress in causing the disorder or in precipitating onset of symptoms Some families do have low blood cholesterol levels and little arterial disease on diets which lead to precocious onset of trouble in many This is true in some strains of rabbits also and in no way disproves the importance of diet as the essential factor which some resist better than others Stress raises blood cholesterol but the widespread atherosclerosis at age 20 in American soldiers is difficult to explain in this group who scarcely knew what socioeconomic stres meant Only if physicians accept the facts made clear by the decisive studies of recent years can the full benefits of the work of Ignatovski and Anichkov lead to a decline in disability and death from arteriosclerosis

Progress in Long Term Management of Coronary Artery Disease is summarized by Mohinder P Sambhi and Henry A Zimmerman[6] (St Vincent Charity Hosp Cleveland) In general management it is important that the patient be educated about the disease and the treatment planned Change of vocation should be advised only when the work would precipitate anginal pain Most physicians allow moderate alcohol and minimum tobacco consumption When anginal pain is definitely related to smoking complete abstinence is mandatory An overweight patient would reduce the work load on the heart by reducing weight and patients with so called calculated normal weight would benefit by an attempt to reduce a few pounds mainly to help regulate and moderate dietary habits

Severe restriction of fat remains a personal decision for every physician Little is known about the biochemistry of normal and degenerating elastic tissue and ground substance The origin of lipids in atheroma remain controversial Human beings maintain a relatively constant level of cholesterol in the blood regardless of the cholesterol intake Recent evidence indicates that incidence of atherosclerosis in various countries roughly parallels percentage of calories obtained *from fats in the diet but no conclusive evidence is*

(6) A M A A h I t M d 101 974 996 M y 1958

monic valves may in some instances be due to presence of anatomically defective valve leaflets which under conditions that lead to dilatation of the ring permit sufficient backflow to result in the sound which is audible over the chest wall

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CORONARY DISEASE

Research in Arteriosclerosis First 50 Years are reviewed by William Dock[5] When Ignatovski of the Russian Imperial Military Medical Academy reported in 1908 that rabbits fed milk and egg yolk acquired severe arteriosclerosis the key was provided to control of a disease which was rapidly becoming more prevalent as living standards rose and infectious diseases killed fewer people Recent extensive studies in Central and North America Africa Europe the Near East Japan and Hawaii have shown that men who consume eggs and milk regularly have higher blood cholesterol levels more severe arterial lesions and higher death rates from coronary disease than those who consume little animal or dairy fat In all warm blooded vertebrates plasma cholesterol rises steeply on diets rich in saturated fats and cholesterol Recent work shows that no foods surpass eggs and butterfat in raising the blood cholesterol of rabbits and man and none have more striking effects in accelerating thrombus formation

The importance of unsaturated fat in protection against arteriosclerosis was first suggested in 1941 by Snapper who contrasted diets and incidence of vascular lesions in Holland and in North China Such fats were proved to lower blood cholesterol

The most convincing proofs that diet causes human coronary disease are studies of severity of lipid infiltration of coronary arteries from birth to old age The greatest annual change in infiltration of the intima occurs in the 1st year of life Cholesterol is also deposited in the intima of suckling rabbits The annual increase in coronary lipid is also high between ages 15 and 30 and only at this time is it much greater in males than in females Autopsies in American men (average age 22) killed in Korea showed grossly visible

(5) Ann I t. M d 49 699 705 S pt mbe 1958

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(6) A M A A Int M 4. 101 974-996 My 1958

available that dietary restriction of fats affects the disease course favorably in an atherosclerotic person Indeed severe dietary restriction under 50 Gm/day is considered unwise and against the principles of good nutrition

Considerable evidence has accumulated that serum cholesterol and phospholipid levels could be lowered by substituting vegetable or nonhydrogenated fats for fats of animal origin This effect could be reversed by hydrogenating the same fats Attempts to lower serum cholesterol and phospholipid levels by adding vegetable oils to a normal nonvegetarian diet have produced equivocal results The formula type diets in which vegetable fats are added to vegetarian diets are unphysiologic

Restriction of fat in the diet may reduce the serum lipid levels in some patients with pathologic lactescence In non lactescent serum a low fat diet seems to be without much effect Some of the levels may be lowered by changing to vegetable oils or administration of vegetable sterols Whether this would ultimately affect the prognosis of coronary artery disease is yet undetermined However most physicians restrict fat in the diet of patients with coronary artery disease

Heparin has been shown to clear alimentary lipemia abolish increased coagulability viscosity and adhesiveness of blood elements and increase the arteriovenous oxygen difference taken from the forearm of patients with atherosclerosis Unless the cost is too great for the patient long term therapy with heparin should be tried Doses of 100 200 mg subcutaneously twice a week do not significantly affect the coagulation mechanism and may have a retarding influence on atherosclerosis

No recommendations can be made for therapy with lipotropic agents vitamins and their relation to atherosclerosis Therapy with effective doses of female hormones carries the risk of permanent and complete castration in males A young man may not accept loss of libido and impotence An older man may undergo mental depression Estrogens are not recommended for treating arteriosclerosis in men in women with coronary artery disease they are justified

Hypothyroidism induced by divided doses of radioactive iodine has been advocated for the patient incapacitated by angina A contraindication is a rapidly progressive disease such as malignant hypertension rheumatic ... After

inducing hypothyroidism small doses of thyroid extract are given sufficient to maintain comfort and to avoid the undesirable effects of hypothyroidism as far as possible

Contradictory reports about the efficacy of various drugs for treating coronary artery insufficiency are confusing Most studies used subjective relief from pain and ECG improvement in exercise tolerance as indications of changes in the coronary blood flow Apparently the effects of cinchona alkaloids were better than those of pentaerythritol and less than those of glyceryl trinitrate Visammin papaverine and aminotrate phosphate are not nearly as useful as nitrites Aminophylline may not be recommended for long term and prophylactic use Anticoagulant drugs are established in therapy of an acute attack or impending myocardial infarction but long term prophylactic anticoagulant therapy in hope of preventing the subsequent episode still awaits conclusive evaluation

Surgical procedures to (1) promote intercoronary anastomosis (2) bring extracardiac blood channels to the myocardium and (3) use the venous end of coronary circulation for perfusion of arterial blood or increase the pressure of backward flow all have surprisingly similar clinical and experimental results The mechanism of improvement underlying all these may be nonspecific to all of them The exact worth of these procedures is still debatable It is difficult to quantitate improvement in any given case It is not valid to predict the disease course nor to presume what might have occurred if the procedure was not done Postoperative results presented by various workers indicate clinical improvement even though it be temporary and nonspecific Interruption of neuronal pain pathways during such procedures may be the direct cause of relief from anginal pain

Association of Specific Overt Behavior Pattern with Blood and Cardiovascular Findings Blood Cholesterol Level Blood Clotting Time Incidence of Arcus Senilis and Clinical Coronary Artery Disease Meyer Friedman and Ray H Rosenman[7] (Mount Zion Hosp San Francisco) studied the possible effect of socioeconomic pressure and stress on the pathogenesis of clinical coronary artery disease in men exhibiting three different overt behavior patterns The men of group A had a behavior pattern primarily char

(7) J A M A 169 1 86 1296 M 21 1959

acterized by intense ambition competitive drive constant preoccupation with occupational deadlines and a sense of time urgency The men of group B had a pattern essentially the converse of that of group A Group C men exhibited a behavior pattern essentially similar to that of group F but with the added elements of a chronic anxiety state

The total calorie and fat intake and the amount of physical activity were approximately the same in all groups and the age height and weight of men were comparable Despite these similarities the average serum cholesterol level was much higher in group A than in the other two groups A hastening of blood clotting time was not observed in all men of group A but only in those with the most fully developed form of the behavior pattern

Clinical coronary artery disease was seven times more frequent and arcus senilis over three times more frequent in group A than in groups B or C

Cigarette smoking exercise working hours alcohol ingestion and heredity per se did not appear to have pathogenic relevance

It is suggested that the behavior pattern exhibited by the men of group A was of itself largely responsible for the higher serum cholesterol and possible hastening of clotting time and also for the markedly increased incidence of both clinical coronary artery disease and arcus senilis Whatever is responsible for behavior pattern A it is neither confined to nor perhaps even more common in any particular echelon of corporate or industrial life

Atherosclerosis in Rhesus Monkeys I Hypercholesteremia Induced by Dietary Fat and Cholesterol George E Cox C Bruce Taylor LaVerne G Cox and Marjorie A Counts[8] (Presbyterian St Luke s Hosp Chicago) with the assistance of Stanley L Cross and William B Wood studied over 30 animals for several months to 3 years Their general health remained excellent

New animals were kept on a stock low fat diet for several months until the serum cholesterol level became stabilized After beginning the experimental high fat high cholesterol diet blood samples were drawn for serum cholesterol and total lipid values and ultracentrifuge study Most animals also had abdominal operations to obtain liver in

(8) A M A A h Path 66 32 52 J ly 1958

testine and skin biopsy for estimation of endogenous cholesterol synthesis and to produce segmental arterial lesions by freezing small discrete areas in the major abdominal arteries Subsequent operations permitted biopsy and histologic study of previously injured vessels Several animals survived 5 or more abdominal operations

The fat diet had to be presented in a form palatable to monkeys By use of a commercial ground monkey food an efficient effective diet was developed as the basic ration to which were added supplements of butter and cholesterol A one food one meal daily technic was useful The experimental diet contained all the nutritional requirements

Serum total cholesterol levels of 300 600 mg /100 ml developed in 1 3 months in most animals tested Some animals showed a high susceptibility to diet induced hypercholesteremia others did not These variations in response are comparable to the clinical variations in man

The hypercholesteremia was interpreted as being chiefly due to excess of dietary cholesterol and not to excess of dietary neutral fat because the serum neutral fat level remained normal or slightly subnormal even in animals with marked hypercholesteremia In addition dietary fat alone without cholesterol produced no significant hypercholesteremia

Grossly and microscopically visible atherosclerosis developed in most animals with cholesterol levels of 300 mg /100 ml or over for several months or longer Intimal lipid deposition was accelerated by subjecting segments of the vessel wall to transient freezing injury Sex apparently did not influence results as moderate to severe hypercholesteremia occurred in both males and females

Changes in Serum Cholesterol and Blood Clotting Time in Men Subjected to Cyclic Variation of Occupational Stress The different incidence of coronary artery disease between American men and women cannot be explained by differences in fat intake Nor is there any clear cut evidence for a sex linked protection against the supposed atherogenic properties of a high fat diet No previous study has considered the possible atherogenic influences of socioeconomic stress

Meyer Friedman Ray H Rosenman and Vernice Carroll[9] (Mount Zion Hosp San Francisco) with the technical col

(9) C culat 17 85 861 M y 1958

laboration of Russell J Tat studied 40 male accountants aged 28 56 who were bled biweekly for serum cholesterol and monthly for blood clotting time from January to June 1957 Accountants were selectively chosen as a self con trolled group for studying the effects of cyclic occupational stress since their routine work schedule is interrupted by urgent tax deadlines

Each was given a mimeographed sheet which provided space for detailed recording of 7 days intake of all foods and beverages at regular mealtimes and otherwise Each subject recorded dietary intake for 1 week each during maximal oc cupational stress and maximal respite

One subject had an acute myocardial infarction and died within 2 hours The other 39 subjects remained in good health Accountants indulge in little physical activity dur ing job stress or respite There were no significant changes in weight physical exercise or dietary intake of calories or fat during periods of socioeconomic stress or respite

Emotional reactions to the periods of stress were obvious The subjects admitted a sometimes overpowering sense of urgency and irritation insomnia nervousness and quarrel someness with family and colleagues and they showed changes in demeanor speech and general attitude

Studied individually each subject s serum cholesterol was consistently highest during severe occupational or other stress and lowest during minimal stress Marked accelera tion of blood clotting time consistently coincided with max imum occupational stress and was normal during respites

These studies indicate an extreme sensitivity of serum cho lesterol to emotional duress The markedly accelerated clot ting time during severe occupational stre s appears as a pos sibly more important phenomenon than elevation of plasma cholesterol

► [It is likely but unproved that emotional stress not only has adverse effects on blood cholesterol and clotting as indicated in this study but also may affect collateral coronary circulation through small but disease free branches

Present evidence indicates that hereditary predisposition and sex are very important factors in the development of coronary atheroma How ever the evidence that diet is also of great importance cannot be ques tioned This study and the preceding one support the common clinical ob servation of the adverse effect of emotional stress There is also strong evi dence that physical exercise taken in proper relationship to the subject s age symptoms and previous habits has a distinctly be[illegible]ect. Tl

probably does not act through any prevention of large branch atheroma but through the encouragement of the development of collateral circulation. In the management of patients with coronary artery disease and for that matter in the management of all men beyond age 40 and women older than 55 these various factors must be considered if patients are to receive the maximum benefit from currently available knowledge —Ed]

Essential Fatty Acids Lipid Metabolism and Atherosclerosis Laurance W Kinsell George D Michaels Roger W Friskey and Stanford Splitter[1] (Highland Alameda County Hosp Oakland Calif) with the technical assistance of George Fukayama H P Chin Marjorie Coelho Sadie Smyrl Florence Olson and Yvonne Fisher studied the effect of low fat diets and different vegetable fats in various patients under controlled observation in the metabolic ward

In 1 patient with familial hypercholesteremia and in a healthy boy polyunsaturated fatty acids per se lowered the plasma cholesterol level as efficiently as did natural fats containing the same amounts of the same acids Studies in a healthy boy showed linoleic acid to be an essential fatty acid in man as it is in the rat Compared with a fat free diet a diet with added ethyl linoleate produced a profound fall in fasting plasma cholesterol neutral fat and phospholipid levels and an increase in net unsaturation of cholesterol ester fatty acids well over the administered material When oleate was substituted for linoleate the plasma cholesterol neutral fat and phospholipid levels slowly rose These characteristic plasma lipid patterns were associated with a deficiency and an abundance respectively of linoleic acid an essential fatty acid

The mechanism by which essential fatty acids lower the plasma cholesterol level is unknown Probably regulation of cholesterol production is involved The fatty acids esterified with cholesterol are predominantly unsaturated normally Triglyceride is probably the donor of fuel fatty acid phospholipid the most metabolically active transporter of fuel fatty acid cholesterol ester a donor of essential fatty acid for new phospholipid synthesis and essential fatty acid a most important part of the phospholipid molecule perhaps in terms of key in lock enzymatic specificity Under usual conditions the turnover of the nonessential fatty acid portions of phospholipid is rapid Turnover of the rest of the lecithin molecule is fairly slow Normally therefore the same molecule of essential fatty acid is conserved and reused many

(1) La t 1 334 339 F b 15 1958

times Essential fatty acids may lower the plasma cholesterol level by decreasing synthesis of cholesterol because the efficiency of the systems is increased

Changes in plasma lipid levels after ingestion of fats containing linoleic acid such as cottonseed soy corn walnut peanut and safflower oils in amounts of 40 180 Gm daily have been observed in 80 patients with various cardiovascular diseases Those with coronary occlusions and cerebral vascular insufficiency feel better those with peripheral vascular disease have shown good symptomatic and functional improvement but none has shown return of palpable pulsation

Diets rich in essential fatty acids appear to be much more effective in lowering plasma lipid levels than are extremely low fat (high carbohydrate) diets Inclusion of adequate amounts of natural fats containing 40 80% linoleic acid in synthetically mixed diets is also effective A phosphatide mixture containing arachidonic acid may be much more potent gram for gram in lowering the plasma cholesterol level than is linoleic acid

Treatment of Angina Pectoris and Other Muscular Pain Due to Ischemia with Iproniazid and Isoniazid is reported by Pedro Cossio (Buenos Aires) in 120 patients with angina pectoris and classic symptoms and ECG changes They were classified as follows grade I patients (65) with symptoms only on selective exertion or violent emotions grade II patients (45) with symptoms on slightest exertion or excitement but still controlled by nitroglycerin and grade III patients (10) with spontaneous prolonged severe pain at any time of day less effectively controlled by nitroglycerin and sometimes requiring morphine At least 1 acute myocardial infarction had been experienced by 37 patients

All had been receiving standard treatment i e restricted effort or complete rest and long acting nitrites plus phenobarbital if no arterial hypotension was present Some were on antithyroid drugs and those with impending myocardial infarction were on anticoagulants One was receiving small doses of thyroid to control myxedema due to I^{131}

Standard treatment was suspended and without altering daily activities 50 mg iproniazid every 8 hours was given to 85 patients and 100 mg isoniazid every 8 hours to the

(2) Am. Heart J 56 113 118 J ly 1958

other 35 for 3 weeks. All patients were then re-evaluated.

In one third of the patients treated with iproniazid and one sixth of those treated with isoniazid attacks subsided entirely or almost entirely after 3-7 days. Another one third and one sixth showed reduction in frequency of attacks of pain to half or less the previous number, and intensity and duration of pain also diminished.

When treatment was interrupted, symptoms almost invariably returned in 1-2 weeks. Substitution of isoniazid for iproniazid brought recurrence of pain in half the patients. In 5% pain recurred despite maintenance on either drug, although with less intensity and shorter duration.

Neither drug had any effect on the natural course of angina pectoris. The ECG changes persisted, progressed or regressed irrespective of variations in pain. During treatment, despite disappearance or attenuation of pain, 1 patient died suddenly and 6 showed acute myocardial infarction. Two thirds of the patients reported side effects, such as faintness, weakness, paresthesia, nervousness, syncope, impotence and muscular twitchings, which were unpleasant but never serious.

Iproniazid and isoniazid should be given in an attempt to prevent anginal pain, regardless of its severity. Success is most likely when the emotional factor is primary and the clinical course least progressive. The drugs may be given singly or with anticoagulants. Nitroglycerin is not contraindicated. Once pain has subsided entirely or almost entirely and the minimal effective dose has been established, treatment must be continued indefinitely on a daily basis.

► [The impressive results reported by the authors have been encountered by others. As yet there is no proof that these drugs have a favorable effect on the underlying disease process. Possibly the action is central and consists in either blocking afferent impulses or in altering the patient's response to such impulses. Nevertheless, the symptomatic results are impressive and it is possible that the relief of pain with the consequent reduction in anxiety may ultimately be shown to have a long-range beneficial effect, not only on the symptoms but also on the disease process.—Ed.]

Hemodynamic Consequences of Coronary Heart Disease With Observations during Anginal Pain and on Effect of Nitroglycerin. It is generally believed that administration of nitroglycerin leads to dilatation of coronary vessels. Increase in coronary blood flow has been shown in animals. Its effect on anginal pain due to coronary heart disease in man has been attributed to its influence on blood flow in the cor

onary arteries but no observations by cardiac catheterization have been reported on the effect of nitroglycerin on left ventricular function and the lesser circulation in man

Ottar Muller and Karl Rørvik[3] (Oslo) performed cardiac catheterization in 24 patients aged 45 84 with coronary heart disease of whom 20 had had myocardial infarction 1 month to 8 years earlier Pressure in the right atrium pulmonary artery and pulmonary capillary pressure were recorded at rest and during exercise and cardiac output was determined by the direct Fick principle Patients with previous infarction an enlarged heart and dyspnea showed signs of left ventricular failure with increased pressure throughout the lesser circulation and a tendency to subnormal cardiac output at rest abnormalities which were accentuated during exercise Pulmonary capillary pressure rose during exercise to levels at which pulmonary edema is imminent and no increase in cardiac output occurred in 2 of 3

Patients with normal heart size and varying degrees of anginal pain showed essentially normal hemodynamics at rest and when free from pain During exercise 9 of 11 showed varying degrees of left ventricular failure with raised pulmonary capillary and/or arterial pressure In patients in whom anginal pain was precipitated by exercise pulmonary capillary pressure rose before sensation of pain appeared

Two patients observed at the height of a spontaneous attack of anginal pain showed transitory gross signs of left ventricular failure with increase of pulmonary capillary pressures to levels at which pulmonary edema may develop It seems therefore that the anginal state generally is combined with varying degrees of left ventricular failure whether pain is precipitated by effort or is spontaneous If precipitated by effort it is usually preceded by signs of left ventricular failure

After nitroglycerin was given to 4 patients with normal heart size while resting on a table the only systematic change was a slight fall (1 2 mm Hg) of pulmonary capillary pressure During exercise before they received nitroglycerin all 4 showed abnormally raised pulmonary capillary pressure and signs of left ventricular failure after receiving nitroglycerin the same or heavier work caused no rise in pulmonary capillary pressure Nitroglycerin did not

(3) Brit. Heart J 0 30 310 July 19 8

significantly change the cardiac output stroke volume or pressure generated in the left ventricle The hemodynamic changes suggest a reserve of coronary vascular capacity re acting to nitroglycerin influencing the function of the left ventricle It is possible that nitroglycerin increases coronary blood flow whether by dilatation of vessels of normal caliber or relaxation of abnormal vasoconstriction remains unknown

► [This study adds strong weight to the exi ting evidence that the con tractile function of the left ventricle is seriously compromised during an ginal attacks and that nitroglycerin has a favorable effect on cardiac contraction under such circumstances Presumably this effect is due to dilatation of coronary vessels However the evidence concerning this point is disputed at present —Ed]

Induced Tachycardia Its Effect on Coronary Hemody namics Myocardial Metabolism and Cardiac Efficiency of In tact Dog was analyzed by George M Maxwell Cesar A Castillo Douglas H White Jr Charles W Crumpton and George G Rowe[4] (Univ of Wisconsin) Induction of tachy cardia changed the general metabolism of the animal only by significantly increasing oxygen consumption When the heart rate rose from an average of 92 to 193 beats per minute this was not associated with any change in cardiac output though the stroke volume decreased significantly There was a small but significant rise in pulmonary arterial pressure as reflected by definite increases in pulmonary arterial re sistance and right ventricular work The tachycardia was associated with a definite fall in left ventricular stroke work Tachycardia thus induced did not change profoundly the sys temic hemodynamics

Although coronary blood flow rose significantly and cor onary vascular resistance fell coronary flow per beat was unchanged No significant difference in oxygen or carbon di oxide contents of the coronary sinus blood was achieved Be cause their arterial counterparts did not change the differ ences between the two did not vary The cardiac metabolic rates for oxygen and carbon dioxide rose significantly but the cardiac respiratory quotient was unaffected The oxygen consumption of the weighed heart also rose significantly In the face of the tachycardia the cardiac oxygen consumption per beat was unchanged The measures of efficiency (index of efficiency ratio of coronary blood flow to left ventricular

(4) J Clin. I t 37 1413 1418 Oct be 1958

work or calculated absolute efficiency) each showed a significant decrease

Hemoglobin and hematocrit values showed no significant change nor did the figures for the pH in the arterial or coronary sinus blood change significantly

Due to the difficulty of measuring the duration of systole in the arterial tracing as obtained by a Cournand needle the tension time index was not calculable If systolic or diastolic systemic pressures measured were multiplied by the heart rate there was a marked increase in these figures in the presence of an induced tachycardia Because neither the systolic nor diastolic pressures changed greatly these products were increased primarily because of the increase in heart rate

It would seem that within limits it is more efficient to deliver the same amount of cardiac work at a slow heart rate than a fast one In the latter circumstance energy is inadequately converted to useful work and must appear in some other form e g heat

► [This report probably carries significant connotations for patients with coronary disease The coronary reserve of the normal heart is great and the increased oxygen need of the heart produced by tachycardia can be readily met When however atheromatous narrowing of the coronary vessels limits increments of coronary flow it is likely that the increased need may not be met Such a conception accords with the general observation that anything which induces a rapid heart rate is likely to precipitate anginal attacks in patients with coronary disease —Ed]

Shoulder Hand Syndrome Following Myocardial Infarction is evaluated by Henry I Russek (USPHS Hosp Staten Island N Y) This syndrome formerly occurred as a complication in 10 20% of all patients with acute myocardial infarction Today it is infrequently observed and rarely reaches an advanced stage Reduction in its incidence and severity is correlated with liberalization of the rigid restrictions of activity in the management of myocardial infarction increasing use of prophylactic measures and new advances in therapy The symptom complex is commonly regarded as a form of reflex sympathetic dystrophy which is initiated and perpetuated by the myocardial infarct Local changes in the shoulder may play a significant role in maintenance of this reflex by contributing to a state of excitation within the spinal cord

When onset is acute or subacute in the early stages of

(5) M Clin N rth America 42 1555 1566 N mbe 1958

shoulder involvement the local signs are similar to those seen in calcific tendinitis In the latter condition exquisite localized tenderness is found over the greater tuberosity and at the subacromial area X rays of the involved shoulder reveal a calcific shadow Onset of hand signs usually resolves any doubts Tenderness of the scalenus muscles along with other points of soreness in the neck and shoulder with weak grip when the hand is swollen may suggest the scalenus syndrome

The best therapeutic results have been derived from cortisone (more recently predni one) and/or ACTH Stellate ganglion block is worthy of trial if steroid therapy proves unsuccessful

With all forms of therapy standard exercises assistive and active should be used in conjunction with other physical therapeutic mea ures such as heat and massage After pain has subsided pulley exercises are especially helpful Until the treatment of choice has been started or has controlled the symptoms analgesics should be given in ample dosage Local injections of procaine at tender points may be effective in some patients Psychotherapy is of distinct value in alleviating the anxiety states or emotional disturbances often associated with the syndrome Because the shoulder symptoms or their severity may be closely bound up with the patient s psychodynamics this form of treatment should not be overlooked

Scalenus Anticus and Related Syndromes result according to I H Upmalis [6] (Univ of Western Ontario) from mechanical interference with the neurovascular bundle of the upper extremity The basic process appears to be intermittent and prolonged stretching and compression of the bundle These forces produce compression of the vasa nervorum with resulting ischemia in the nerve bundles Lesions thus produced are not circumscribed Concerning the pathogenesis there are two schools of thought vascular signs and symptoms are produced by direct pressure on the subclavian or the axillary artery or vascular changes are produced by irritation of the vasomotor nerves within the brachial plexus or adjacent to it

Diagnosis may be difficult Age of onset is 20-60 Only one or both *arms may be involved Onset may be associated with*

(6) S g Gy & Ob t. 107 521 5 9 Dec mbe 1958

some unusual or strenuous physical exertion involving the upper extremity The commonest symptoms are pain and paresthesia in the upper extremity associated with numbness and clumsiness in the affected extremity Distribution is chiefly in the area supplied by the ulnar nerve though patients often complain of pain at the base of the neck In early stages the symptoms are vague There may be no findings on physical examination If present they may include impairment of touch pain and temperature senses to variable extent mainly on the medial aspect of the forearm and hand Muscular atrophy may be of median or ulnar type Vascular symptoms occur in about half the patients Tenderness over the scalenus anticus muscle is a relatively constant finding X ray examinations are of value in showing abnormalities of the bones in the neck and of the thoracic operculum

Physiotherapy aimed at strengthening the trapezius muscle gives gratifying results in about 70% of the patients Surgery is indicated in patients with definite neurologic or vascular changes in the extremity or in those who fail to respond to conservative management No single operation will relieve symptoms in all patients The surgical procedure should be suited to the anatomic situation encountered

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HYPERTENSION

Eighteen Pheochromocytomas Clinical Aspects and Surgical Results E Dahl Iversen[7] (Univ of Copenhagen) treated 8 men 8 women and 2 boys aged 10 and 15 who had pheochromocytoma Duration of the disease until surgery was 2 months to 14 years in 17 patients and 30 years in 1 patient Paroxysmal hypertension was present in 12 During attacks systolic blood pressure rose from 230 to 300 mm Hg and diastolic from 135 to 140 Sustained hypertension was noted in 5 patients The retinas were normal in 11 patients whereas 7 had hypertensive retinopathy varying from grade II to IV apparently independent of the duration of the disease and the type of hypertension The amount of total adrenaline in the urine was examined in 13 patients In those with paroxysmal hypertension the amount was between 206 and

(7) Acta h a d 116 118 131 1958 59

3 800 μg /24 hours and in those with permanent hypertension it was between 800 and 3 100 μg /24 hours

The number of eosinophils was determined in 10 patients 7 of whom had paroxysmal hypertension Eosinophil counts were normal in 6 In 3 patients counts were made in connection with an attack and the number of eosinophils was 0 Blood sugar was increased in 10 patients varying between 112 and 224 mg /100 ml BMR was increased 125 190% in 7 of the 18 patients The histamine provocative test performed in 7 patients was positive in 5 The benzodioxan or Regitine® test used in 5 patients during attacks was positive in all

Retroperitoneal precoccygeal pneumography combined with tomography was used in 10 patients and showed the tumor distinctly in 9 in 1 of these the tumor was bilateral

Signs of renal failure resembling tubular necrosis (lower nephron nephrosis) developed in 3 patients in connection with attacks in 2 after they received 300 mg cortisone in the course of 36 hours preoperatively

The pheochromocytoma was removed in 15 patients in 14 it was intra adrenal and in 1 ectopic Mortality was nil The other 3 patients (1 with intra adrenal and 2 with ectopic pheochromocytoma) were so ill that they died before the tumor could be localized or removed

After surgery blood pressure was normal in 11 of 14 patients and ranged from 150/95 to 160/100 in 3 After average follow up of 4 3 years 13 of 15 patients had normal blood pressure No hypertensive attacks occurred after surgery

► [The measurement of urinary catechols is technically difficult but has been shown repeatedly to be of value in the diagnosis of pheochromocytoma The following abstract indicates that in collecting urine for such measurements the posture of the patient should be taken under consideration.—Ed.]

Effect of Body Posture on Urinary Excretion of Adrenaline and Noradrenaline was studied by Tage Sundin[8] (Karolinska Inst Stockholm) Tilting of healthy subjects from recumbency to +75 degrees induced rise in mean noradrenaline excretion from the preceding recumbency value of 9 8 to 34 1 μg /minute (procedure 1) Urinary output of adrenaline increased slightly during tilting at +25 degrees but rose significantly at angles of +50 and +75 degrees

In other subjects catechol excretion was determined in

(8) Acta med scandinav vol 161 pp 336 1958

recumbency and tilting in head up position to +75 degrees during the same hours on different days (procedure 2) Noradrenaline increased from 16 5 to 55 8 μg/minute Even in recumbency after tilting noradrenaline excretion was substantially increased (27 9 μg/minute) though significantly less than the tilting value The output of adrenaline rose from 4 8 during recumbency to 7 3 μg/minute

Tilting according to procedure 1 was accompanied by marked fall of systolic blood pressure only at +75 degrees but no significant change in diastolic pressure occurred at any tilting angle Pulse rate increased significantly at +75 degrees The smaller increase in pulse rate in the group studied according to procedure 2 was attributed to the subjects better physical condition and to different initial conditions

Increase in urinary output of adrenaline is ascribed to the general stress involved in standing The much larger increase of noradrenaline in urine is ascribed to blood pressure homeostatic reflexes stimulating noradrenaline producing vasomotor nerve endings

After administration of a ganglion blocking agent to healthy subjects noradrenaline excretion during tilting at +75 degrees was only 12 9 μg/minute as compared with 55 8 in untreated subjects Adrenaline output at +75 degrees did not differ from that in untreated controls This low noradrenaline excretion is ascribed to decreased endogenous production of noradrenaline due to blocking of the synapses to postganglionic vasomotor nerves Blocking could not have been complete however because the pulse rate rose during tilting

Patients with essential hypertension when tilted to +75 degrees showed pronounced fall of systolic blood pressure and moderate increase in pulse rate whereas diastolic pressure remained more or less unchanged Mean systolic pressure however remained elevated during tilting as compared with the group of healthy subjects

Method for Electrocardiographic Recognition of Atrial Enlargement New criteria have been delineated by Radi Macruz Joseph K Perloff and Robert B Case[9] (Nat l Inst of Health) in a study of 110 patients with congenital and acquired heart disease using the relation among durations of P wave P R segment (time between end of electric atrial systole and onset of electric ventricular systole) and P R interval (time between beginning of electric atrial systole and onset of electric ventricular systole) Precise physiologic data were available in all cases

The accepted range of normal for the P R interval is so broad that many patients with atrial enlargement fall within it The P wave duration alone is not helpful However by the ratio of the P R interval occupied by the P wave expressed as $\frac{\text{P duration}}{\text{P R segment}}$ atrial enlargement can be more precisely recognized Normally the P duration is 50 60% of the P R interval for all heart rates The ratio is within the narrow limits of 1 1 6

In right atrial enlargement the P R segment increases because of an increased transit time from the sinoatrial to the atrioventricular node The P duration remains constant hence the P PR ratio falls below normal range When the right atrium is sufficiently enlarged it may write the terminal portion of the P wave thus prolonging the P duration as well as the P R interval hence increasing both numerator and denominator resulting in a normal P PR ratio Thus if the P PR ratio is normal and the P R interval prolonged the associated finding of a P duration which though prolonged does not exceed 0 1 second below age 16 years and 0 12 second above 16 suggests the presence of right atrial enlargement

In left atrial enlargement the terminal portion of the P wave is delayed because of the prolonged transit time of depolarization through the enlarged left atrium Hence P wave duration is prolonged the P R segment is shortened and the P R interval remains unchanged The result is a P I R ratio above the normal limit of 1 6

(9) Circulation 17 882 889 May 1958

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is as follows Hyperventilation precipitates at least two series of events based on respiratory alkalosis and autonomic stimulation With production of a period of respiratory alkalosis ions may be exchanged across the cell membrane As the blood pH rises potassium ions may leave the cells This potassium shift would account for the temporary increase in serum potassium If such change occurs in the myocardial cells significant increase in the potassium concentration of blood from the coronary sinus would be expected is was shown in 1 of the authors patients

Innocent Inversion of T Wave of Electrocardiogram W A Seldon (St Vincent s Hosp Sydney) calls attention to the fact that an ECG taken after ingestion of 100 Gm glucose will show flattening or inversion of the T waves It is possible that a high carbohydrate meal could produce similar results However it is doubtful if this is of practical importance Of more significance is the flattening of the T waves as an effect of fear which has been observed in healthy individuals by several authors

Acute emotional stress will cause increased sympathetic activity and a sudden fall in blood pressure acts similarly However less acute psychic strain will do the same Any maneuver which causes increased sympathetic tone leads to flattening or inversion of the T wave such as the effect of standing upright administration of drugs causing a rapid fall in blood pressure and intravenous infusion of epinephrine It is likely that fear acts through the same mechanism In the case of drug administration a reflex increase of sympathetic tone occurs to stabilize the falling blood pressure with resultant T wave inversion as after inhalation of amyl nitrite Similar T wave inversion has been noted during the hypotension which followed intravenous injection of 4 mg reserpine in a healthy young adult male When performing experiments of this type the author noticed that induction of a T wave inversion was easier in some subjects than in others

Although a deeply inverted symmetrical T wave is characteristic of ischemic heart disease T waves which are flattened diphasic or slightly inverted may be physiologic variants Ultimate correct diagnosis will depend on serial tracings and an accurate assessment of a detailed history plus

(2) M J A t I 2 154 156 A g 2 1955

In combined atrial enlargement the right atrium continues to prolong the P R interval and the left atrium prolongs the P wave The P PR ratio may be normal If such is found and the P R interval and P wave are prolonged combined atrial enlargement can be suspected

These criteria apply regardless of age group to conventional scalar ECG s They can be used without modification for routine clinical purposes

Electrocardiographic Changes in Hyperventilation Syndrome Possible Mechanism and Clinical Implications Paul N Yu and Bernard J Yim[1] (Univ of Rochester) investigated 16 women and 4 men aged 20 55 with the hyperventilation syndrome Only 1 had organic heart disease a small interatrial septal defect In each sinus tachycardia and abnormal ECG changes were observed during hyperventilation The commonest change was T wave inversion which was present in 15 patients In 2 S T segments were depressed and in 2 others amplitude of the T wave was reduced and the Q T interval markedly prolonged In 1 patient an initially inverted T wave became upright during hyperventilation

No significant change was found in serum sodium chloride calcium and transaminase Arterial blood oxygen saturation and tensions were usually slightly higher during hyperventilation than during control periods There was little or no change in the oxygen capacity of the blood The average arterial pH rose significantly from 7 40 to 7 56 and the average Pco consistently fell from 42 to 24 mm Hg The average serum potassium level rose during hyperventilation with room air from 4 to 4 5 mEq /L During hyperventilation with 6% carbon dioxide however these measurements generally approximated those observed during the control period Inhalation of 6% carbon dioxide prevented the ECG changes in all but 1 patient

Potassium chloride 20 mEq diluted in normal saline infused intravenously over 20 minutes completely prevented the changes during hyperventilation in 4 patients and partially in 1 other In 5 patients 20 μg epinephrine injected intravenously produced ECG changes similar to those observed during hyperventilation with room air A tentative explanation for the ECG changes during hyperventilation

(1) T A. Am Phy a 71 129 141 1958

leads which display the major changes because of their near ness to the 0 point

Special caution is suggested in interpreting serial changes in precordial leads especially when they occur in or near the transitional zone

► [This abstract and the 2 preceding ones illustrate the error in basing a clinical diagnosis on minor electrocardiographic changes and especially on alterations in the amplitude and direction of T waves Minor T wave changes occurring in the absence of clinical evidence of some organic dis ease of the heart should be disregarded entirely Alterations in serial electrocardiograms should be taken seriously only when minor changes in the position of the precordial electrode are excluded. This can readily be done by recording from multiple interspaces in a given vertical line. Similarly the effects of respiratory variations must be eliminated before one ascribes too much significance to changes in serial records in the amplitude of the QRS deflection —Ed]

PHYSIOLOGY AND CONGESTIVE HEART FAILURE

Critical Review of Recent Work on Ventricular Diastolic Suction is presented by Gerhard A Brecher[4] (Emory Univ) Many have postulated that intraventricular diastolic suction somehow contributes to ventricular filling Often the idea is expressed as active diastole and diastolic vis a fronte This has been based mainly on reasoning from meager or even no evidence

During diastole the ventricle atrium and adjoining veins form a common cavity If pressure in the ventricle is lowered by some force below that which would exist in the absence of such force this may be called suction Vis a fronte is a frontally acting force which draws blood from various parts of the circulatory bed toward the ventricle Three factors contribute to this force (1) thoracic aspiration by which blood flows from the extrathoracic into the thoracic veins (2) ventricular contraction which lowers atrial pressure and contributes to atrial filling and (3) diastolic ventricular vis a fronte which concerns ventricular filling directly

At present the following unequivocal experimental evi dence is available in favor of the existence of a ventricular diastolic vis a fronte (1) In the beating mammalian and rep tilian heart fluid can be drawn into the ventricular cavity in

(4) C culat Res. 6 554 566 S ptembe 1958

physical findings and if necessary laboratory and radiologic aids

Positional and Respiratory Changes in Precordial Lead Patterns Simulating Acute Myocardial Infarction Abnormal ECG patterns may be produced by a variety of factors Exercise eating smoking change in posture and change in respiratory rate or level frequently affect the T waves and S T segments *In* left ventricular hypertrophy right ventricular hypertrophy complete or incomplete left and right bundle branch block and cardiac displacement QS deflections and/or significant Q waves occur frequently in leads V_3 and V_4 and less often in leads V_5 and V_6 These patterns may suggest myocardial infarction in the absence of an actual lesion

Thomas August Alberto Mazzeleni and Louis Wolff[3] (Beth Israel Hosp Boston) observed 3 patients whose ECG s displayed precordial QRS T changes which simulated those of acute myocardial infarction These changes were found to be produced by respiration or slight shifts in the position of the exploring electrode

The orientation and magnitude of the cardiac vector were not significantly altered and were not responsible for the ECG changes which occurred with respiration Alterations in the conducting medium secondary to pulmonary aeration were not likely involved as the ECG changes were confined to small localized areas overlying the heart and were not accompanied by vectorcardiographic changes

The major determinants of the configuration of a given QRS complex in a unipolar lead are (1) the position and distance of the exploring electrode in relation to the electrical center of ventricular depolarization (0 point) (2) the orientation and magnitude of the cardiac vector and (3) the conducting medium A change in one or more of these factors will alter the ventricular complex and all must be considered in a possible explanation of the changes effected by respiration

Whether the change of spatial relationship between the 0 point and the electrode during respiration is due to a shift of the chest electrode secondary to thoracic motion or to a change in the anatomic relations of the equivalent dipole is unknown probably both are involved It is the precordial

(3) Am H rt J 55 706 714 M y 1958

can be done however in a relatively short time so that recordings can be made before the subject has recovered from the exercise Besides the aorta itself plays a secondary role in adjusting the flow of the cardiac contents for optimal use by the peripheral working muscles

Electrokymographic studies of the aortic knob and ascending aorta regions were performed in 13 champion athletes and 20 untrained healthy medical students The recordings were made with the subjects standing and immediately after a 1 minute exercise Simultaneous phonocardiograms and electrocardiograms were recorded

The results revealed a direct relationship of the isometric contraction and the rapid ejection phases with the cardiac cycle length The reduced ejection phase although it changed during exercise showed no relationship to the cardiac cycle length but was inversely related to the rapid ejection phase

Within the accuracy of the measurements the protodiastolic phase (closure of the semilunar valves) showed no constant change or relationship to various cardiac cycle lengths

An evaluation of the electrokymographic tracings of the aortic knob was attempted by calculating the ratios of the amplitudes at the lowest point of the incisura and at the summit of the dicrotic wave to the maximal ejection amplitude The difference between these two ratios was then compared with the change in cardiac cycle length The measurements revealed that the amplitudes of the incisura and of the rebound wave are largely dependent on the cardiac cycle length and its variation

The dicrotic wave disappeared after exercise in 9 of the 13 athletes whereas the same took place in only 4 of the 20 untrained subjects This observation is also characteristic of the recordings of patients with cardiac insufficiency

Gallop Rhythm in diastole is discussed by James V Warren James J Leonard and Arnold M Weissler[6] (Duke Univ) The ventricular gallop sound often called a protodiastolic or rapid filling sound usually occurs about the end of the first third of diastole It is a low pitched short sound best heard near the apex or between that point and the pulmonic area It is often enhanced by maneuvers which increase the murmur of mitral stenosis as when the patient

(6) A I Med 48 580 596 M h 1958

the absence of a positive ventricular filling pressure provided the ventricle is nearly empty (2) In nearly empty ventricles negative transmural (subatmospheric) pressures can develop during diastole (3) Greater negative ventricular pressures are preceded by stronger systolic contractions (4) Elastic forces in the walls of quiescent nearly empty ventricles produce negative transmural ventricular pressures (5) Part of the vis a fronte is produced by elastic recoil of the ventricular walls which tend to assume their diastolic filling state after the end of systole (6) The amount of fluid drawn into the ventricle is larger during diastoles which follow strong systolic contractions than during diastoles which follow weak systolic contractions (7) Ventricles which eject their contents against a resistance can draw fluid into their cavities in the absence of a positive filling pressure (8) Epinephrine increases the amount of fluid which can be drawn without positive filling pressure into a ventricle which ejects against resistance (9) The contribution of the vis a fronte to ventricular filling is about 10% of the estimated resting cardiac output in turtle ventricles working against a load which corresponds to that of normal aortic pressures in that species

However it is not known how much ventricular filling is caused by a diastolic frontal force under normal physiologic conditions There is no evidence that the ventricles are expanded by some myocardial contraction or by an active decontraction or by filling of the coronary tree

Electrokymographic Studies of Movements of Aortic Wall in Champion Athletes E Linko S Kajas K Hartiala and R Vasama[5] (Univ of Turku) call attention to the fact that electrokymographic analyses have given valuable information on the time relationships of the cardiac function and also on the condition of the contractile elements of the cardiac wall This technic has also been used in studies of the aortic wall From these latter tracings it has also been possible to estimate the cardiac cycle phases

Electrokymographic studies on the ventricular part of the heart give direct information on the time relationships of the cardiac cycle It is however technically rather difficult to perform such analyses in a working subject The accurate and correct placing of the pick up device in the aortic region

(5) An med int F e 47 7 22 1958

sult of atrial contraction in presystole (atrial gallop) When both sounds are present a quadruple rhythm results

Effect of Acute Hypovolemia on Release of Aldosterone and on Renal Excretion of Sodium was studied by Daniel Fine Leonard E Meiselas and Theresa Auerbach[7] in 2 normally active healthy persons—a man and a woman Bioassay of salt retaining activity of the urine was based on the effect of injected extracts on the urinary potassium sodium ratio of adrenalectomized rats

Acute reduction in blood volume resulted in moderate con ervation of sodium and water by the kidney a less intense and le s consi tent increase in potassium excretion and a fairly consistent elevation of urinary aldosterone excretion The altered electrolyte excretion could be attributed to modification of renal tubular function Serum sodium and potassium levels and endogenous creatinine chromogen clearances remained constant The quantitative relation between increase in aldosterone in the urine and modified electrolyte excretion suggests that the increased aldosterone was causal and not merely coincident Urinary aldosterone is assumed to reflect the level of circulating aldosterone

Urinary aldosterone excretion rose without concurrent rise in other urinary corticosteroids This dissociation resembles that seen in many situations where an intense stimulus for sodium conservation exists It is probably due to increased adrenal secretion of aldosterone This is independent of ACTH secretion and of the potassium sodium ratio in the serum

When hemodilution occurred spontaneously consistent reduction of urinary sodium excretion and consistent elevation of urinary aldosterone excretion were noted These changes also occurred when the blood volume was rapidly restored by immediate infusion of 25% salt poor human albumin Blood loss and the associated hemodilution process may initiate changes that may be monitored in the extra and intravascular spaces culminating in renal conservation of sodium probably in part due to accelerated tubular reabsorption of this ion

► [Th s report and the 3 which follow it illustrate some of the advances being made in the study of the complex mechanisms responsible for disturbed fluid and electrolyte balance in pat ents with heart failure The prec mechanism *responsible for sodium retention is still debated.* The

(7) J Cl I est. 37 232 243 F bru ry 1958

turns on the left side and after a brief exercise period This sound is of quite low frequency and as in the murmur of mitral stenosis it is heard best with the bell of the stethoscope with care taken not to press too firmly on the skin Tension caused by the stethoscope makes the skin act as a diaphragm and it filters out the low frequency sound

A ventricular gallop appears in patients with incipient or actual congestive heart failure However a similar sound (3d heart sound) may be heard on occasion in normal persons—hence a diastolic sound does not necessarily mean heart failure even when heard in a patient with heart disease

An atrial (presystolic) sound is the gallop most frequently heard in patients with hypertension myocardial infarction and complete or partial heart block In contrast to the ventricular gallop the atrial sound is frequently not associated with impending or actual heart failure and therefore has a different clinical significance It is best heard near the left sternal border in the 5th interspace although at times it is loudest at the apex Because of the low frequency of the atrial sound it too is visualized and palpated much more readily than it is heard

Another diastolic sound is heard in patients with pericardial disorders and is often called a pericardial knock In general it occurs earlier than does the gallop is of a higher frequency has a striking respiratory component is transmitted widely and may even exceed the other heart sounds in intensity

The opening snap of the mitral valve is short and higher in pitch than the other gallop sounds and is heard best in the 3d or 4th interspace to the left of the sternum There is an inverse relationship between its time of onset and the pressure gradients across the mitral valve An opening snap should not be confused with a gallop sound

In young people there may be a relative delay in closure of the pulmonic valve in relation to the aortic valve This causes slight splitting of the 2d heart sound as it is heard in the pulmonic area Even with wide splitting this sound is seldom confused with a gallop because the sounds are of the same pitch

Gallop sounds are related to the termination of the two phases of rapid ventricular filling The first occurs in protodiastole (ventricular gallop) and the latter occurs as a re

This sequence of events is attributed to sustained production of antidiuretic hormone invoked by some extraosmoreceptor mechanism when cardiac output becomes inadequate for metabolic needs of the body

Hyponatremia the clinical state associated with a lowered concentration of sodium in the plasma is discussed by Jack Orloff MacKenzie Walser Thomas J Kennedy Jr and Frederic C Bartter[9] (Nat l Inst of Health) Exclusive of hyperglycemia and hyperlipemia the finding of a lowered concentration of sodium in plasma is always indicative of dilution the relative retention of water in excess of solute in the body The common denominator in all cases of hyponatremia must then be an inability to excrete ingested water with sufficient rapidity to maintain a normal osmotic pressure

Most if not all cases of dilution hyponatremia may be considered as being the result of a disturbance in one or more of the following factors (1) filtration rate (2) volume flow to the loops of Henle and the distal convoluted tubule (3) reabsorption of sodium and anion in this area with resultant freeing of water and (4) permeability of the tubule membrane to water in the diluting area

Inadequacy of filtration causes hyponatremia in a nephrectomized animal and in an anuric patient and is at least a contributory factor in patients with renal insufficiency in whom the number of functioning nephrons is reduced In the latter group when filtration rate is seriously depressed and insufficient urine is delivered to the diluting site the relatively small volume of urine that can be excreted may be insufficient to overcome dilution produced by intravenous administration of fluids In some instances hyponatremia may develop on what otherwise would be considered a normal fluid intake Admittedly an added factor in these patients may well be persistent antidiuretic hormone (ADH) secretion

Dilution hyponatremia may also occur as a result of a reduction in volume flow to the diluting segment not necessarily secondary to a decrease in the number of functioning nephrons

A reduction in capacity of the distal segment to reabsorb sodium and thereby to free water may be a significant factor in adrenal insufficiency as well as in cases of chronic ne

(9) C rculat 19 84-299 F bru ry 1959

evidence in these papers would suggest that alterations in extracellular fluid distribution may be of major importance The studies also indicate that water retention may occur independently of decline in sodium excretion —Ed]

Pathogenesis and Treatment of Hyponatremia in Congestive Heart Failure are described by Raymond E Weston Jacob Grossman E Raymond Borun and Irwin B Hanenson[8] In the past the primary role of sodium retention in the pathogenesis of cardiac edema has been generally accepted because of the therapeutic success of the low sodium diet and of measures for promoting sodium excretion and the apparent ability of most cardiac patients to excrete even large amounts of fluid when maintained on restricted sodium intake However metabolic studies from several laboratories have revealed that not infrequently the weight gained or lost by cardiac patients during the development or mobilization of edema is greater than can be explained in terms of sodium balance alone These observations and reports that the urine of edematous cardiac patients may contain increased quantities of antidiuretic material have led to reinvestigation of the older notion that in certain phases of congestive failure there may be water retention in excess of sodium

The authors studied the development of such primary water retention in cardiac patients in whom chronic congestive failure was acutely intensified by escape from digitalization development of digitalis toxicity or severe acute respiratory infection It was observed that acute intensification of chronic congestive failure in cardiac patients on low sodium diets may lead to continued water retention with increasing edema and hyponatremia without external sodium loss This sequence is illustrated by the events after development of severe respiratory infections or escape from digitalization in such patients Such sequence may occur also at times in the presence of ECG changes suggestive of digitalis toxicity but actually due to potassium depletion

This clinical course is not favorably influenced by intravenous administration of isotonic or concentrated sodium solutions However increasing cardiac output by adequate digitalization or decreasing body metabolic demand by treatment of the underlying infection may lead to increased water excretion in excess of sodium decreased body weight and restoration of more normal serum electrolyte concentrations

(8) Am J Med 5 558 572 Oct be 1958

above or below the hepatic veins and irrespective of changes in vascular volume

The precise changes that accompany acute loss of fluid and electrolytes from the blood stream and stimulate aldosterone production remain obscure The mechanism does not seem to be effected by increased secretion of ACTH because corticosterone output was decreased after acute thoracic caval constriction

Observations on Prolonged Administration of Amisometradine (Rolicton*) an oral nonmercurial diuretic to 106 patients with congestive heart disease and 12 with premenstrual tension involving salt and water retention are presented by Edward Settel (Brooklyn) All cardiac patients (59 class III and 47 class IV) were fully digitalized and their salt intake was restricted to 1 5 Gm daily Initial dosage for patients who had not received oral diuretics previously was approximately 1 or 2 400 mg tablets 4 times daily The dose was reduced to the lowest effective maintenance level as soon as dry weight was achieved The cardiac patients who were receiving other diuretic medication previously were given 1 400 mg tablet 2-4 times daily All 12 patients with premenstrual tension were given 3 400 mg tablets daily for 10 days preceding expected menstruation and their salt intake was restricted to 1 2 Gm daily

In addition to amisometradine two thirds of the patients observed were given mercurial diuretics parenterally 3 8 times monthly

The effectiveness of the drug was determined by (1) reduction of edema (2) ability to maintain near dry weight consistently and for long periods (3) reduction in the requirement of parenteral mercurials (4) ability to retain electrolyte balance of body fluids (5) absence of acute or chronic toxicity and (6) subjective comfort of the patient When all these requisites were met fully the response was classified excellent The response was excellent in 55% of the patients good in 27% and poor in 18% Of the entire series the class IV cardiac group showed the highest average of good and excellent response

The number of required mercurial injections for patients who had not been on other diuretics was reduced about 60% In contrast this number was reduced only 25% for the pa

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2) Am P t & D gest T 10 479 483 M rch 1959

phritis associated with increased rates of salt excretion In both the sodium reabsorptive capacity of the distal segment is decreased despite adequate flow to this area and consequently solute free water may not be formed in large amounts Both these clinical situations may also be complicated by an associated fall in extracellular fluid volume and filtration rate Whether *persistent* secretion of ADH may also be an important factor is not certain

Increased Aldosterone Secretion Following Acute Constriction of Inferior Vena Cava James O Davis Bernard Kliman Nicholas A Yankopoulos Ralph E Peterson and Alfred Casper[1] (Nat l Inst of Health) point out that aldosterone secretion and excretion in urine are markedly elevated in dogs with chronic ascites secondary to thoracic caval constriction It has been suggested that the adrenal cortex is stimulated to secrete aldosterone by factors resulting from high venous pressure and the consequent loss of fluid and electrolytes from the blood stream

The effects of acute constriction of the thoracic inferior vena cava and of the abdominal inferior vena cava above the adrenals on aldosterone corticosterone and Porter Silber steroid secretion in adrenal vein plasma of dogs were studied Of 7 dogs with thoracic caval constriction 3 received dextran intravenously to maintain or increase plasma volume After three control determinations 30 minutes apart six to eight measurements were made at similar intervals during the experimental period After thoracic caval constriction alone aldosterone secretion increased within 30 minutes and reached levels two to fourfold greater than the average control rates of 0 008 0 024 μg /minute Corticosterone and the Porter Silber steroid output remained unchanged or decreased Plasma volume was reduced Similar increases in aldosterone secretion occurred despite increased vascular volume secondary to infused dextran in 3 other animals with thoracic caval constriction Of 4 dogs with abdominal caval constriction 2 showed increased aldosterone secretion This occurred only after pronounced caval constriction and large sustained increments in venous pressure The experiments showed that increased aldosterone secretion occurs after acute constriction of the inferior vena cava

(1) J Cl I t 37 1783 1790 Decembe 1958

above or below the hepatic veins and irrespective of changes in vascular volume

The precise changes that accompany acute loss of fluid and electrolytes from the blood stream and stimulate aldosterone production remain obscure The mechanism does not seem to be effected by increased secretion of ACTH because corticosterone output was decreased after acute thoracic caval constriction

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In addition to amisometradine two thirds of the patients observed were given mercurial diuretics parenterally 3 8 times monthly

The effectiveness of the drug was determined by (1) reduction of edema (2) ability to maintain near dry weight consistently and for long periods (3) reduction in the requirement of parenteral mercurials (4) ability to retain electrolyte balance of body fluids (5) absence of acute or chronic toxicity and (6) subjective comfort of the patient When all these requisites were met fully the response was classified excellent The response was excellent in 55% of the patients good in 27% and poor in 18% Of the entire series the class IV cardiac group showed the highest average of good and excellent response

The number of required mercurial injections for patients who had not been on other diuretics was reduced about 80% In contrast this number was reduced only 25% for the pa

(2) Am Pract & Digest Treat 10 479 483 March 1959

tients who previously had been on other oral diuretics Class III cardiac patients were usually maintained on 1 400-mg tablet daily and class IV cardiac patients on 3 400-mg tablets daily for long periods without increasing the number of mercurial injections

No toxic effects on hemopoietic renal or hepatic function were seen

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MISCELLANEOUS

► A few years ago this editor could find only a small number of important publications dealing with cerebral vascular disorders Happily this situation is now reversed Presumably the increasing interest in this subject is due to the expanding therapeutic implications of dietary anticoagulant and surgical management Another encouraging trend is the renewed progress in auscultation as a consequence of the correlation of bedside observations with phonocardiography That the rapid progress of previous recent years in the fields of congenital disorders cardiac surgery and atheromatous disease continues is well illustrated by the abstracts to follow —Ed

Auscultation of the Heart Aubrey Leatham[3] (St George s Hosp London) reports that the graphic registration of heart sounds and murmurs has greatly facilitated analysis of their pattern timing and relation to demodynamics

The 1st and 2d heart sounds (valve closure sounds) must be interpreted in the light of asynchrony between the two ventricles causing splitting of sounds Knowledge of the degree of splitting of the 2d sound and its behavior during respiration is of great diagnostic value Atrioventricular valve opening sounds are always abnormal an obvious mitral snap is diagnostic of mitral stenosis and is seldom absent in that disease Early systolic ejection sounds indicate dilatation of the aorta or pulmonary artery Triple or gallop rhythm is due to accentuation of ventricular filling vibrations Atrial sounds indicate increased resistance to ventricular filling most commonly from hypertension and the 3d sound due to rapid ventricular filling is exaggerated when atrial pressure is abnormally high from ventricular failure or constriction or atrioventricular regurgitation in the absence of stenosis Extracardiac sounds occur about mid or late systole after ejection when the heart is moving in relation to other structures but no valve movements are taking place

(3) La et 2 703 708 Oct 4 757 765 Oct 11 1958

Murmurs are related to flow of blood which is initiated by changes in pressure Moments of change in pressure are signaled by the heart sounds to which the onset crescendo and cessation of the murmur can be related Systolic murmurs fall into two main groups ejection and regurgitant according to their shape and relation to the heart sounds Murmurs which continue throughout systole and diastole are caused by the continuous flow of blood from a higher to a lower pressure area and are distinguished from ejection murmurs by their great intensity at the end of systole Murmurs during ventricular diastole may be classified by their timing and relation to the heart sounds as ventricular filling atrial systolic (presystolic) and regurgitant diastolic

► [Because of limitations of space it is not possible to indicate in a brief abstract the clinical significance of these observations The author has learned to apply at the bedside information previously available only from phonocardiograms Every physician concerned with auscultation of the heart should study in detail Leatham s splendid reports—Ed]

Systolic Murmurs according to Aubrey Leatham[4] (St George s Hosp London) may be classified as (1) midsystolic ejection murmurs caused by the foward flow of blood through the aortic or pulmonary valves and (2) pansystolic regurgitant murmurs due to backflow of blood from ventricles to atria through incompetent valves or from left ventricle or aorta to a relatively low pressure right ventricle or pulmonary artery through a ventricular septal defect or patent ductus arteriosus respectively In patent ductus arteriosus (or aortopulmonary septal defect) as in ventricular septal defect the type of murmur depends mainly on the size of the communication and the relation between pulmonary and systemic resistances

Sounds of aortic and pulmonary closure are identified by consideration of their site of maximum intensity direction of transmission and behavior during respiration Aortic closure is normally transmitted to all areas and is entirely responsible for the 2d sound at the apex Pulmonary closure is softer and localized in the pulmonary area or nearby it is delayed during inspiration and causes splitting of the 2d sound in the pulmonary area Aortic thus precedes pulmonary closure in normal subjects Increased stroke volume stenosis or complete (not incomplete) bundle branch block delay valve closure on the affected side

(4) C cula 17 601 611 Ap 1 1959

Ejection murmurs are caused by flow of blood through the aortic or pulmonary valves under the following conditions stenosis of valve or infundibulum increased rate of ejection through the valve valvular damage without stenosis dilatation of the vessel beyond the valve and combinations of these factors

With valvular or infundibular stenosis the duration of systole of the affected ventricle is prolonged and the crescendo of the murmur may appear to be late and may even obscure the sound of semilunar closure of the unaffected side of the heart The murmur however always ceases before the delayed semilunar closure of the affected side The short crescendo about midsystole is an invariable feature of all ejection murmurs

Precordial Murmurs during Pregnancy and Lactation Various innocent murmurs may develop during pregnancy and are often attributed to heart disease J Willis Hurst Jean Staton and David Hubbard (Emory Univ) report 2 cases In 1 patient the precordial systolic murmur due to an arterial bruit persisted after delivery but vanished after lactation ceased The murmur was heard with maximum intensity just left of the midsternum It undoubtedly was due to a bruit in a branch of the mammary artery A palpable artery was found in the 3d left intercostal space near the sternum Occlusion with a finger caused the murmur to disappear instantly The murmur decreased in intensity the artery became smaller and the left breast became smaller when the baby was allowed to nurse from the left breast only once a day The murmur completely disappeared the artery ceased to pulsate and the left breast returned to normal size when the baby was weaned

In the other patient a precordial continuous murmur originated in the large dilated veins of the breast and could be altered by firm pressure with the stethoscope bell

Cardiovascular Dynamics of Bowel Function Straining at stool has been associated with angina and sudden death and has been invoked as a cause of myocardial infarction pulmonary embolism hemorrhage at the base of the skull and spontaneous rupture of the spleen Alfred Halpern Norman Shaftel David Selman and Herbert G Birch[6] deter

(5) New Engl d J Med 259 515 517 Sept 11 1958
(6) Angiology 9 99 111 Apr 1 1958

mined intrathoracic and arterial pressure circulation time and heart rate and took ECG s in several hundred patient observations The patients were all presumably normal except some had chronic constipation About 12% of straining episodes were sufficiently intense and prolonged to satisfy the accepted criteria for the Valsalva maneuver When a bedpan was used instead of a commode 28% of strainings met the criteria Constipation increased this frequency to 58%

Blood pressure changed during defecation straining in those episodes severe enough to fulfill the criteria of the Valsalva maneuver The height of the initial blood pressure rise was roughly proportional to the intensity of the effort in both constipated and unconstipated subjects but the former had twice as many peaks above 60 mm Hg

The Valsalva maneuver initiated ECG changes in about 20% of the normal subjects including S T depression flattening of the T wave and poststraining arrhythmia and reversal of a previously abnormal T wave in 1 person These abnormalities are generally associated with physiologic myocardial insufficiency

Certain straining efforts were associated with tachy or bradycardia Such alterations of heart rate are reflexes principally associated with the Valsalva phenomenon

Straining at stool is potentially hazardous in patients with cardiac disease The physiologic changes of straining may have serious consequences To avoid tragic episodes constipation in the patient with cardiovascular disease should be corrected immediately

► [These studies supply additional information concerning the hazards of prolonged and rigid rest in bed especially when coupled with the use of the bedpan for defecation —Ed]

Nonpenetrating Traumatic Injury of Heart Loren F Parmley William C Manion and Thomas W Mattingly[7] (Armed Forces Inst of Pathology) reviewed 546 autopsy cases representing 0 1% of 207 548 autopsy cases available for study Mechanisms producing nonpenetrating injuries to the heart are direct indirect bidirectional or compressive decelerative blast concussive and combined

Incidence can be only estimated because mortality rate is low and morbidity generally minimal Autopsy and clinical series vary from 10 to 75% Cardiac injury is often over

(7) C lat 18 371 396 S pt mbe 1958

looked because other bodily injury often masks the manifestations In most of the 546 cases other bodily injury was so severe that the patient would have died in the absence of cardiac lesions Direct nonpenetrating cardiac trauma seldom produces serious consequences unless the myocardium is ruptured or fatal arrhythmia develops

Parietal pericardial hemorrhage was often associated with other traumatic lesions of adjacent mediastinal structures and heart Hemorrhagic manifestations varied from small punctate hemorrhages to large hematomas several centimeters in diameter Parietal pericardial lacerations occurred in 249 cases were single or multiple and a few millimeters to 10 cm or longer In some pericardial disruption was so extensive that the heart ruptured into one of the pleural cavities usually the left side Hemorrhage into the pericardial sac was frequent In the acute form the sac was distended with blood which was often partially clotted and the source of the hemorrhage could usually be demonstrated

Pericarditis was noted occasionally When it was associated with lesions of the e ophagus or adjacent mediastinal structures the pericardial cavity sometimes became infected Cardiac hemorrhage or contusion was recognized as a dark red hemorrhagic area in the wall of the heart If the hemorrhage reached or involved the endocardium even in absence of laceration mural thrombi occasionally formed

Lacerations with contusions occurred in 64 Hemorrhage along a major branch of a coronary artery was frequent In immediately fatal lesions microscopic findings were hemorrhage with extravasation of red blood cells disruption and fragmentation of the heart muscle With survival of an hour or over mural thrombi formed in some instances in which the endocardial surface was lacerated Leukocytic infiltration was present in the first few hours The heart ruptured in 353 cases Contusion or laceration was the only cardiac lesion in 105 Death was the immediate result of trauma in 67 cases but in only 12 was the primary cause of death injury to the heart

Extensive and severe cardiac contusion and laceration from nonpenetrating trauma may occur without external evidence of chest injury Signs or symptoms may be absent or masked by other injury They may mimic myocardial infarction of coronary artery disease in character and inten

sity of pain its radiation and duration Pain may not be immediate but may occur several hours or days later and may often be prolonged Occasionally angina pectoris may follow such injury If it persists coexistent coronary artery disease probably is responsible The ECG abnormalities are conduction disturbances arrhythmias or QRS abnormalities In most cases only transitory nonspecific abnormalities of the S T segment and T wave are noted but these are not unequivocal since they may be produced by a multiplicity of noncardiac causes Their presence should point to the possibility of cardiac injury Late complications of cardiac contusion are cardiac aneurysm calcification of the injured myocardium rupture of an extensively contused area of myocardium and mural thrombi

Most patients with cardiac contusion do not require specific treatment but only immediate restriction of activity and continuous observation Prognosis is good Morbidity is slight and recovery usually complete Bed rest for 2 weeks or if contusion is extensive for 3 4 weeks suffices Precordial pain almost constant is usually relieved by mild analgesics Oxygen therapy is almost specific to relieve pain and reduce dyspnea and cyanosis Should true myocardial failure develop prognosis is poor Anticoagulant therapy is not indicated because of danger of hemorrhage in traumatized areas specifically increasing threat of serious hemopericardium

Nonpenetrating traumatic injury may produce coronary thrombo is but this is rare except in pre existent coronary disease Coronary artery laceration or rupture is not rare A common result of myocardial injury is production of arrhythmias particularly those of supraventricular origin Atrial fibrillation or flutter is probably the commonest Ventricular tachycardia or fibrillation may be the mechanism of death in some instances

Permanent or serious disability is rare Every measure should be taken to prevent neurosis for many persons are susceptible to iatrogenic disease whether or not they are conscious of the possibility of a disability claim The problem of aggravation of pre existent disease by trauma is most difficult in medicolegal evaluation of traumatized patients

► [One frequently encounters patients with ECG evidence of an old nonprogressive focal myocardial lesion but without any clinical manifestations of cardiac disease The common tendency to ascribe almost automatically such ECG changes to silent infarction and to restrict the activities

is without justification Many such patients have a story of a steering wheel injury to the chest or of trauma to the precordial region when boxing or playing football Cardiac contusion is probably a common cause of abnormal ECG s in persons whose hearts are clinically and functionally normal —Ed]

Syndrome of Suspended Heart is evaluated by Bertram A Bradlow and Monty M Zion[8] (Univ of Witwatersrand) Evans and Lloyd Thomas have shown an association of certain specific ECG abnormalities with a particular radiologic configuration of the heart The ECG reveals abnormal S T segments and T waves suggesting infarction of the lateral and posteroinferior portions of the left ventricle or of left ventricular strain without abnormal voltages Radiologic examination shows a heart that during deep inspiration appears suspended between the vascular pedicle above and the inferior vena cava below The authors observed the syndrome in a girl aged 12 a woman 24 and a man 41

Evans and Lloyd Thomas believed that separation of th suspended heart from its close contiguity with surrounding structures particularly the diaphragm disturbs the anatomic medium that customarily transmits the varying electric potential generated by cardiac contraction causing changes a sociated with this characteristic ECG

In some patients posturing might alter the anatomic relation of the heart to its environs In 1 of the authors patients in sitting position with the legs horizontal the T wave previously inverted became upright In another patient squatting diminished the degree of abnormality The relation of the heart to its environment particularly the diaphragm may be the factor concerned in causing the ECG abnormality Whether this is due to disturbance of the transmission of electric potential or to alteration of the direction of the repolarization vector remains a matter for conjecture

The authors observed patients with similar radiologic appearances of their hearts but with normal ECG s In patients with normal ECG s the anatomic relationships of the heart may be different from those of persons with the abnormal ECG of the suspended heart syndrome

True incidence of this syndrome in a population cannot be known without mass surveys but recognition of the benign nature of the ECG findings is important for reassurance of the patient and for the question of insurance

(8) Lancet 2 501 503 Sept 6 1958

Amyloidosis of the Heart was noted by R M Mulligan[9] (Univ of Colorado) in 17 of 1 150 autopsies in patients aged 70 or over The sex ratio of 16 men to 1 woman when corrected to the sex ratio of the total study population became 6 4 1 No chronic suppuration or plasma cell myeloma were found Review of the literature shows that amyloidosis of the so called primary type is more widespread in body organs and tissues before age 70 after which it tends to be localized to the heart and to be commoner in men

Symptoms of cardiac amyloidosis include dyspnea orthopnea cyanosis and cough Signs include low blood pressure peripheral edema anasarca rales in the lungs normal or hypertrophied heart systolic murmur distant or muffled heart tones accentuated pulmonic 2d sound and atrial fibrillation The cardiac failure does not respond to treatment as readily as that in arteriosclerotic heart disease or essential hypertension

Of the 17 patients 15 were under normal in height and weight Other evidences of malnutrition included absent teeth low hemoglobin value and red cell mass Chest x rays showed a normal or hypertrophied heart infiltrations in the lungs indicating pulmonary edema and cloudy costophrenic angles denoting hydrothorax The ECG findings included atrial fibrillation left ventricular strain left axis deviation inverted or flat T wave increased P R interval notched QRS atrioventricular block bundle branch block prolonged atrioventricular conduction time and premature ventricular contractions The principal changes were low voltage delayed intraventricular conduction partial atrioventricular block and alterations suggesting myocardial ventricular damage or infarct

Amyloid appearing most often as gross granules in the atrial endocardium and as granules or diffuse infiltrations of the myocardium of all chambers was less common in the epicardium and valves In size the hearts were normal to strikingly hypertrophic Coronary arteriosclerosis was usually minimal to moderate and nonocclusive The amyloid deposited in the myocardium predominantly among the muscle fibers and capillaries was metachromatic with methyl violet or crystal violet variably red with Congo red and a distinct shade with ammoniacal silver

(9) A M A Arch Path 65 615 630 J 1958

Amyloidosis regardless of localization is probably secondary to a disturbance of blood protein levels in which hyperglobulinemia is paramount

Control of Complete Heart Block by Use of Artificial Pacemaker and Myocardial Electrode A serious complication of reparative surgery of atrial and ventricular septa is complete heart block often resulting in death due to low output failure Any method that increases the heart rate for a sustained period is likely to be effective therapy Drugs particularly isopropylarterenol have helped but individual response is unpredictable Electric stimulation of the heart by external electrodes is excellent in theory but introduces many practical difficulties keeping the electrodes in place painful skeletal muscle contractions burns and especially in children severe apprehension

William L Weirich Matthias Paneth Vincent L Gott and C Walton Lillehei[1] (Univ of Minnesota) placed a fine insulated wire into the myocardium of dogs in which complete heart block had been experimentally induced Complete control of the ventricular rate was achieved by connecting this wire to an electric pacemaker and completing the circuit by placing a flat indifferent electrode about 1 2 cm in diameter on or under the skin approximately over the left ventricle Low currents induced myocardial contractions but were apparently imperceptible to the dogs

The method was used in 18 patients The voltage output of the pacemaker had to be 1 5-4 5 volts and currents had to be less than 13 5 40 5 ma One patient s heart was stimulated for 21 consecutive days before pacemaker support could be safely discontinued No detectable sensations contractions of skeletal muscle burns infections or other complications occurred

The myocardial electrode is a fine silver plated copper wire It is inserted into the right ventricular wall by being wedged on a needle The needle is then cut off and the electrode fixed by two fine silk stitches The wire is insulated by threading it through appropriately sized polyethylene or Teflon tubing The electrode is easily removed by simple traction The indifferent electrode is implanted subcutaneously over the apex of the left ventricle

This method effectively controls the heart block which

(1) Circulation Res 6 410-415 July 1958

often develops after closure of atrial and ventricular septal defects and has been the single most important contribution to the rapidly decreasing mortality of open heart surgery

Syncopal Attacks Following Quinidine Administration A case is reported by F Gerard Allison[2] (Winnipeg)

Woman 40 had successful commissurotomy for pure mitral stenosis and auricular fibrillation Six months later conversion was attempted with quinidine Small doses were given without effect except for mild vomiting After a total of 1 6 Gm the patient vomited all night and had some diarrhea Next morning she had three brief episodes of unconsciousness One was observed Pulse and blood pressure disappeared but rapid heart sounds were heard An ECG showed a normal rhythm of 40 plus an equal number of ventricular extrasystoles (pulsu bigeminus) The S T intervals sagged due to digitalis or low potassium The Q T interval was markedly prolonged Since the last dose of quinidine had been taken 14 hours earlier the changes were considered to be due to hypopotassemia brought on by the quinidine induced diarrhea and vomiting which had caused digitalis intoxication leading to ventricular paroxysmal tachycardia and syncope Treatment was with Pronestyl® chlorpromazine and potassium chloride The rhythm reverted to normal and the patient became asymptomatic

Potassium and procaine amide is the best treatment for digitalis intoxication When a patient reacts with vomiting or diarrhea to a small dose of quinidine it is wise to prevent these symptoms by giving paregoric before larger doses are administered This allows administration of therapeutically effective doses and prevents unpleasant side effects and loss of potassium in vomitus or stool

Staphylococcic Bacteremia and Endocarditis is discussed by Richard H Meade III[3] (Boston Univ) In patients with staphylococcic bacteremia the symptoms may be due to (1) the primary infection (2) bacteremia entirely (3) the metastatic suppurative lesions (4) a combination of the three or the symptoms may be masked by a coexisting disease or suppressed by therapy administered in treatment Manifestations of the infections range in degree from mild to fulminant

Acute infective or ulcerative endocarditis usually the result of staphylococcic valvulitis connotes a rapidly progressing destructive lesion on the heart valve with acute onset of fever and even prostration and an early fatal outcome Occasionally staphylococcic infections of the endocardial surfaces may evolve slowly and produce few symptoms other

(2) C ad M A J 78 949 950 J 15 1958
(3) C rc l t 19 440 457 M b 1959

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(3) C l t on 19 440 457 M h 1959

than occasional fever for periods of months The acute di ease may be converted into a subacute process by suppressive antibiotic therapy

Two features of staphylococcic endocarditis are of partic ular importance the propensity of the organism to invade normal heart valves and the frequency with which only the right side particularly the tricuspid valve is involved Al though antibiotics are responsible for reducing the incidence of pneumococcic or gonococcic endocarditis both of which may involve undamaged valvular surfaces they have not so affected the incidence of staphylococcic infection

Penicillin is the drug of choice for management of infec tions developed outside the hospital in the absence of specific knowledge of the organism s sensitivity because 90% of the strains thus acquired are susceptible Penicillin must be given intramuscularly or intravenously and the aqueous crystalline benzyl salt of sodium or potassium should be used

If infection had developed in the hospital it is not safe to assume that either penicillin or streptomycin will be effec tive Presently most hospital strains are sensitive to chlo ramphenicol and erythromycin The latter is the better agent however staphylococci may become resistant if the drug is used by itself Chloramphenicol suppresses the rate with which this occurs The dose of the two is the same (50 75 mg /kg)

DISORDERS OF THE PERIPHERAL VESSELS

Nature and Treatment of Septic Shock William A Altemeier and William R Cole[4] (Univ of Cincinnati) describe a treatment schedule by which 16 of 41 patients in septic shock were saved (1) Immediate intravenous infusion of fluids particularly plasma or blood was carried out to correct any deficiency of the circulating blood volume without overload ing the circulation (2) Massive doses of antibiotics were given intravenously These were often selected empirically until reports of bacterial cultures and sensitivity to the anti biotics were obtained The existence of shock made the intravenous route advisable because of the impairment of

(4) A M A Arch Surg 77 498 507 Octobe 1958

absorption urgent need for rapid therapeutic effect and the overwhelming nature of the infection (3) Arterenol was given in 5% solution of dextrose in water by intravenous drip regulated to restore the blood pressure to 80 mm Hg or above This was done in an effort to maintain the various essential physiologic functions particularly renal filtration until the infection was brought under control The drug was discontinued only after the blood pressure could be main tained without it (4) An indwelling catheter was used to measure hourly urinary output which was maintained be tween 25 and 75 cc /hour by regulated administration of ar terenol and fluid (5) Oxygen was given continuously by nasal catheter or tent (6) The foot of the bed was elevated 12 18 in (7) Cortisone or hydrocortisone was withheld un less it was impossible to restore or maintain the blood pres sure by use of fluids and arterenol Under this circumstance the steroid hormones were used in an effort to extend the patient s life until the severe infection could be controlled by intensive antibiotic therapy and any indicated surgical treat ment (8) Timed surgery was carried out when indicated and feasible

Experience has confirmed the wisdom of infusing the ar terenol through indwelling polyethylene tubing as a means of preventing local cutaneous gangrene Use of the intrave nous route for administration of antibiotics in large doses appeared particularly efficacious in controlling the infection but 2 7 or more days were required for this effect

Pathology and Management of Chronic Ischemia of Lower Limb G E Mavor[5] (Aberdeen Royal Infirm) ana lyzed 266 cases of peripheral ischemia affecting the lower limb and found that in 90% the cause was atherosclerosis (atheroma) with secondary thrombosis The principal changes in atheroma occur in the intima fatty acid and cho lesterol accumulations and subintimal hemorrhages The media also becomes thickened and fibrosed however giving pathologic justification for use of the term atherosclerosis As a result of the intimal disturbance the artery becomes narrowed and eventually thrombosed Although atheroma may sometimes be generalized in the arterial tree the throm bosis is at first localized or segmental

Anatomically atherosclerosis can be divided into two

(5) J R y C ll S geo Ed b gh 3 264 85 J 1958

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(4) A M A A ch S g 77 498 507 O tober 1958

protection of the limb and prevention of joint deformity More specific measures entail induced vasodilatation and anticoagulant therapy Even when surgery is done many of these conservative measures are of value both before and after operation In many instances direct surgery gives greater palliation than any other method of treatment Lumbar sympathectomy is a valuable indirect procedure Gangrene is no longer an absolute indication for amputation In about 25% of patients with gangrene of the foot and toes due to arterial disease the limb can be saved and amputation limited to one or several toes by an arterial reconstruction operation

► [It would seem that the conservative management of occlusive vascular disease is effective in a large percentage of patients Frequent walking vasodilator drugs anticoagulants and the same dietary regimen used in treating coronary disease are important measures Surgical treatment should be reserved for patients with advanced disease or for those who fail to respond to these procedures Walking is especially important. —Ed.]

Peripheral Vascular Diseases are discussed by Robert R Linton[6] (Harvard Med School) Although diet and atherosclerosis appear to be somewhat related further studies are necessary to determine this fact The fundamental laboratory procedures (oscillometry digital plethysmography skin temperatures and walking tests still remain the important methods of study of the peripheral blood flow Sympathectomy for the present has been replaced by arterial reconstruction and grafting procedures

Reconstructive arterial surgery cannot be accomplished satisfactorily without visualization of the arterial tree in the lower limb by injection of a radiopaque solution into the arterial system proximal to the major diseased area

Arterial and aortic homografts make satisfactory replacements in man if immediate and early results alone are considered In most instances in which various synthetic fabrics have been used as aortic and arterial grafts the follow up period has not been sufficiently long to determine whether these materials are satisfactory for long term use

Late failures in homografts have been due mostly to degenerative changes in the graft or infrequently to failure to obtain an adequate inflow of arterial blood at the proximal anastomosis either because it was not placed sufficiently

(6) N w E gla d J Med 260 27 8 F b 5 32 3 8 F b 1 370 375 F b. 19 1959

groups—main vessel disease in which the aorta iliac femoral or popliteal arteries are affected and small vessel disease in which the anterior or posterior tibial arteries or those of the foot are involved In the author s series which does not include diabetics of 244 patients with atheroma and secondary thrombosis 223 had main vessel occlusions The vessels distal to the popliteal artery were the initial site of thrombosis in only 21 The commonest site of occlusion was the femoral artery

In diabetics arterial disease often presents as gangrene and the underlying pathologic process is usually small vessel atheroma with thrombosis

The term arteriosclerosis is used to describe changes in the medial coat of an artery Pathologically the lesion is a medial sclerosis and in its severest form hyalinization and calcification may occur As the arterioles are involved hypertension is common Thrombosis is not a feature as the intima remains intact The artery therefore remains patent and even when degeneration is advanced there may be no peripheral arterial insufficiency Arteriosclerosis is often associated with atheroma—not an unexpected finding as the former becomes to some extent universal and the latter is very common In this event when the arteriosclerotic vessel becomes occluded the process is begun by atheroma and completed by thrombosis

Thromboangiitis obliterans may present a problem in differential diagnosis mainly because it is still probably inaccurately regarded as a main vessel occlusive disease The entity has been described as an ascending small vessel arteritis which affects the lower limb and eventually becomes bilateral

In direct trauma damage to an artery may be severe enough to initiate a thrombosis Dislocations simple fractures and penetrating and gunshot wounds may be complicated by thrombosis Traumatic arteriovenous fistula also leads to peripheral ischemia

In the assessment of the patient s condition arteriography is essential and management usually depends more on its results than on any other factor Certain general therapeutic measures are important such as maintenance of a normal blood pressure and hemoglobin level control of infection relief from pain and provision of rest by sedation adequate

procedure are dependent on location extent and nature of the occlusive process and certain systemic factors Lumbar sympathectomy is considered a desirable supplemental procedure if there is associated peripheral disease with secondary narrowing or occlusion in the smaller distal arterial bed

Surgery restored pulsatile circulation through the major arterial channels in about 95% of patients with aortoiliac occlusive disease Associated cardiac and renal disease constituted the major cause of the 12 (2 7%) operative deaths Occlusion recurred in only 8 patients in 3 27 months after operation Successful restoration of circulation was obtained by a second operative procedure consisting of a bypass graft

Of 353 patients with occlusive disease of the femoral artery 317 were treated by the bypass graft Excision and graft replacement (done on 19) has been virtually abandoned in favor of this procedure Endarterectomy (done on 17) is still considered desirable but its indications are infrequently encountered Normal pulsatile circulation was restored in 84% of the group Occlusion recurred in only 41 patients 3 weeks to 38 months after discharge A second operation was performed on 27 of the 41 with late failure with successful restoration of circulation in 20

Clinical Significance of Raynaud s Phenomenon and Raynaud s Disease is summarized by Ray W Gifford Jr[8] Raynaud s phenomenon is the commonest vasomotor disturbance affecting the extremities Unlike Raynaud s disease it is not a distinct clinical entity for it may be encountered as a symptom of various diseases and conditions Episodes of Raynaud s phenomenon are always intermittent lasting from a few seconds to a few minutes rarely longer They are usually confined to the fingers or toes or both and seldom involve the hand feet ears nose and lips Typically one or more fingers or toes acquire a deathly pallor or livid cyanosis when the extremities are exposed to cold environmental temperatures or when the patient becomes emotionally overwrought Sometimes the pallid phase gives way to the cyanotic phase The pallid phase is due to spasm of small arteries and cutaneous arterioles leading to complete though temporary occlusion The cyanotic phase is due to incomplete occlusion The episode is sometimes terminated by the rubor phase

(8) M Cl North Am 4 963 9 0 July 1958

far cephalad or because the host artery was not endarterec tomized to obtain adequate arterial inflow In a few cases failure was due to a poor runoff

The number of successful aortic and major artery embolec tomies has increased greatly in the past few years Success has also been obtained in late peripheral embolism by retro grade flushing with a dilute heparin solution to clear the arteries of the secondary thrombi that form distal to the embolus in addition to an embolectomy A few years ago this would not have been considered possible because of the distal propagated thrombus formation The scope of embo lectomy has also been extended to the smaller arteries such as the popliteal and superior mesenteric with good results

The surgical treatment of varicose veins has generally re turned to a radical stripping to remove the long saphenous vein from the groin to the internal malleolus and the short saphenous vein when involved from the popliteal space to the external malleolus The general trend in the treatment of deep venous thrombosis is anticoagulant therapy

Surgical Considerations of Occlusive Disease of Abdom inal Aorta and Iliac and Femoral Arteries Analysis of 803 Cases is reported by Michael E De Bakey E Stanley Craw ford Denton A Cooley and George C Morris Jr[7] (Hous ton) Experience in this series established the concept that the obstructing lesion in chronic arteriosclerotic occlusive disease of the lower extremities is usually well localized and segmental with a relatively normal patent lumen above and below the occluding lesion

The cases were classified into two categories aortoiliac occlusion and femoral occlusion In the former group of 448 cases 44% were characterized by complete aortic occlusion and 56% by incomplete occlusion Associated occlusive dis ease of the peripheral arterial bed was present in 18% and was more frequently encountered in patients with incom plete aortic occlusion These findings point to the importance of arteriographic studies in providing precise knowledge concerning the location and extent of the occlusive process to permit effective therapy

The following surgical procedures were used to restore normal circulation thromboendarterectomy excision with graft replacement and bypass graft The indications for each

(7) Ann S g 148 306 324 S ptembe 1958

Aortography is most useful when small abdominal aneurysms are suspected The technic requires only rapid injection of about 20 ml opaque medium into the upper part of the abdominal aorta A single x ray of the abdomen 14×17 in is taken at the end of the injection The actual size of an aortic aneurysm is not always apparent in the aortogram because the lumen of the aneurysm usually contains a variable amount of clot

Renal arteriography is of value in the study of intrarenal tumors and cysts anomalies of the renal blood supply occlusive lesions of the renal arteries and a hydronephrotic kidney The technic of retrograde aortography by femoral artery catheterization is particularly applicable to renal arteriography

Among over 2 000 aortograms performed there were no fatal complications Serious complications without permanent ill effects included anuria and ileus pneumothorax chylothorax and esophagitis

Isolated Angiography with Catheter Inserted Percutaneously Its Indications and Results are summarized by G Gollmann[1] (State Hosp Graz Austria) Percutaneous angiography is technically feasible causes the patients but few complaints and complications need not be expected In each easily accessible vessel the catheter may be advanced proximally or distally and the contrast medium applied directly to the study area A small amount of contrast medium is required for aortography through the femoral artery 20 cc of 50 70% medium usually suffices With the aid of a guiding wire it is possible to reach through the femoral artery individual branches of the aorta

Angiography is not limited to the demonstration of vascular changes The shape and location of the vessels and passage time of the contrast medium through them gives information on the respective organs themselves Blastomas can be demonstrated if they have specific vessels or if these contrast by filling defects In many instances angiograms help to differentiate between benign and malignant tumors Vascular new formations of normal configuration normal course of the visualized arteries capillaries and veins and good delineation of the tumor against its surroundings point to a benign lesion *Atypical blood vessels blood pooling with*

(1) F rtsch Geb Rö tg trahlen 89 383 396 Oct be 1958

Raynaud's phenomenon may appear after sudden arterial occlusion due to thrombosis or embolism especially in the upper extremities It is often associated with and may be the first manifestation of rheumatoid arthritis and scleroderma Repeated trauma to the hands and fingers in certain types of occupations may lead to occlusion of the palmar arterial arch or its digital branches with secondary Raynaud's phenomenon and ischemic lesions at the finger tips The various shoulder girdle compression syndromes including scalenus anticus syndrome with or without cervical ribs hyperabduction syndrome and costoclavicular syndrome may produce Raynaud's phenomenon presumably by irritation of the compressed sympathetic nerve fibers

Allen and Brown proposed that Raynaud's phenomenon must be present for at least 2 years in the absence of conditions or disease to which it may be secondary before a valid diagnosis of Raynaud's disease can be made Follow up studies show that the diagnosis of Raynaud's disease established by these criteria is accurate in 95%

Abdominal Aortography According to Owings W Kincaid and George D Davis[9] (Mayo Clinic and Found) the simplest method of abdominal aortography is the translumbar

TECHNIC.—In routine study of occlusive vascular disease two aortic punctures are used With the first the needle is introduced into the aorta at the level of the 12th thoracic vertebra and 18 20 ml is injected rapidly in 4 5 seconds a single film being exposed at the end of the injection This film will show the condition of the entire abdominal aorta and its visceral branches and often the iliac arteries as well If the condition of the lower part of the aorta permits a second needle is inserted well below the origin of the renal arteries just above the bifurcation of the aorta Injection at this level permits good visualization of the femoral arteries The authors inject 35-40 ml opaque medium through this needle slowly for 10 12 seconds and expose the film at the end of the injection This exposure is made on two films 14×17 in that lie end to end in a special cassette 14×36 in In a person of average height this single exposure will show the vascular tree from the site of injection in the lower part of the aorta down to and including the trifurcation of the popliteal arteries When examination of only a specific branch of the abdominal aorta is desired selective retrograde aortography performed through a catheter inserted in the femoral artery and passed upward into the aorta to or just above the origin of the branch to be examined is an excellent method

(9) New England J Med 259 1017 10 4 Nov 20 1067 1 1958

that block sympathetic activity at different sites does not increase cerebral blood flow and vascular resistance diminishes only in proportion to the drop in blood pressure No information is available on the effects on cerebral circulation and metabolism of altering blood coagulability by anticoagulant medication except for some observations indicating that heparin caused no change in the cerebral circulation of elderly patients

Cerebral vascular resistance may be decreased in the presence of increased or decreased blood carbon dioxide content increased or decreased blood pH and increased unchanged or decreased arterial carbon dioxide tension Of the various drugs used in treatment of cerebral vascular lesions only papaverine and carbon dioxide by inhalation actually produce vasodilatation

That the brain can alter the local blood supply according to the needs of the tissues is evident If such a regulatory mechanism is effective it might be anticipated that local deprivation of blood flow as in thrombosis or embolism of a cerebral vessel would provide the maximal stimulus for increasing local circulation It is known that anoxia increases cerebral blood flow and that a form of reactive hyperemia also occurs in the brain

Spontaneous Strokes in the Young Harold Stevens[3] (George Washington Univ) observed spontaneous strokes in 32 healthy normotensive subjects aged 5½-44 years None had traumatic neoplastic infectious embolic or other primary disease Two large etiologic groups were identified those due to cerebral venous thrombosis and those due to *cerebral arterial thrombosis Of the latter 16 were observed* some due to carotid artery thrombosis Diagnosis of carotid artery thrombosis can often be made by clinical observation including a history of acute onset of headache with contralateral hemiplegia and ipsilateral Horner s syndrome Palpation of the carotid artery and ophthalmodynamometry are valuable but not infallible technics Arteriography is often indispensable particularly to exclude intracranial aneurysm or tumor but unnecessary painful or dangerous tests can often be circumvented by careful analysis of clinical data

In differential diagnosis syphilis and hypertension are readily eliminated Brain tumor collagen disease and

(3) A I t. M d 49 10 2 1034 N mbe 1958

fast filling as in arteriovenous fistulas and poorly delineated tumor borders indicate malignancy

In renal angiography the isolated contrast filling of the renal artery leads to better visualization of the small terminal branches which are poorly demonstrated by aortography Unilateral angiography protects the opposite kidney and prevents superposition of vessel shadows on the visualized kidneys

Introduction of the catheter into the celiac artery makes possible splenoportography through the splenic artery Injection of contrast medium into the splenic artery will visualize the spleen and splenic and portal veins There are several advantages of splenoportography through the splenic artery over transparietal splenoportography complications due to improper placement of the needle and bleeding from the injection canal are avoided the entire spleen including anastomoses with the vena cava at the upper and lower poles of the spleen may be visualized and early space occupying lesions in the pancreas can be demonstrated by simultaneous filling of the splenic vein and artery

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CEREBRAL VASCULAR DISEASE

Critical Review of Circulatory Physiology as It Applies to Cerebral Vascular Disease is presented by Peritz Scheinberg (Univ of Miami) Aging results in decreased cerebral blood flow and increased cerebral vascular resistance Patients with known cerebral vascular disease show these changes but to what extent is not yet clear There is no definite evidence to indicate that patients with clinical cerebral vascular disease with or without current neurologic changes show alterations in cerebral circulatory and metabolic functions beyond that seen in patients of similar age without evident vascular disease of the brain There is no satisfactory explanation for the occasional occurrence of thrombosis of one internal carotid artery without development of neurologic deficit

The sympathetic nervous system does not greatly influence cerebral vascular resistance or blood flow Use of drugs

(2) An I t M d. 48 1001 1016 M y 1958

vascular tree to arterial spasm or in hypertension to small hemorrhages In most cases the underlying cause is athero sclerosis The extent of collateral pial circulation from the anterior and posterior cerebral arteries which may supply the area of cortex normally supplied by the middle cerebral artery suggests cerebral va cular insufficiency rather than vasospasm as the cause The arteries are narrowed or oc cluded often at a point remote from their terminal dis tribution This leads to the brain tissue becoming dependent for its blood supply on collateral branches from neighbor ing vessels This supply is adequate for ordinary purposes but falls below the critical requirement if systemic blood pressure suddenly falls or if the collateral vessel itself narrows

In the normal subject the vascular fields supplied by the two carotids and basilar artery remain distinct except at their periphery where they mingle at an arteriolar level However only 50% of Willis circles are normal Defects in the po terior communicating arteries are e pecially fre quent The vessels which form the circle are particularly prone to the premature changes of atheroma Atheromas have special preference for the carotid vertebral and cere bral arteries The carotid and vertebral systems are com parably affected In studying the consequences of occlusion in either system caroticobasilar insufficiency should be considered

Insufficiency and occlusion of the internal carotid is com moner in men than in women and more prevalent on the left side than on the right Most cases occur in the 5th 7th dec ades but a significant number arise in young adults The clinical picture resembles that of occlusion of the middle cere bral artery for which it is often mistaken There may be transitory numbness or weakness of one hand Diagnosis can sometimes be confirmed by palpating the vessels in the neck or from the pharynx or by finding a decrease in the ar terial blood pressure in the optic fundus demonstrated by digital or instrument pressure on the eye during ophthal moscopy Absolute diagnosis is made by carotid angiogra phy or surgical exploration Obstruction is usually at the level of the bifurcation of the common carotid or within 3 cm above i

congenital and acquired diseases of the vascular and hematologic systems are then sought The multiple tests necessary to investigate these various possibilities are usually negative The time consumed however is often sufficient to permit spontaneous improvement Erroneous diagnosis of multiple sclerosis is then often made by exclusion

Most spontaneous (arterial) strokes in the healthy young are due to solitary atheromatous plaques similar to those found in older patients Stress seems to precipitate the attack in some patients The usefulness of anticoagulants in treatment or prevention of stroke requires further validation Prognosis in these selected patients was generally good with no specific treatment Indiscriminate use of anticoagulants without proper refinement of the heterogeneous diagnosis of stroke is hazardous Increased bleeding into a hemorrhage infarct is a particular danger

Further study of strokes in the healthy young would be particularly rewarding because the causative lesion can be studied in pure culture without contamination of the issue by the diffuse and multiple degenerative changes that accompany strokes in elderly patients

Cerebral Vascular Disease in Light of Modern Technics is reviewed by J St C Elkington[4] (Nat l Hosp London) The toll of this disease surpasses that of arteriosclerotic heart disease and carcinoma of the bronchus and lung The cerebral disorder is arterial hypertension also known as hypertensive encephalopathy may occur with severe hypertension from whatever cause—essential hypertension unilateral renal disease toxemia of pregnancy or rare disorders such as porphyria Symptoms are mental and physical and fluctuate in severity Anxiety confusion merging into delirium and alterations of consciousness are conspicuous General or focal epileptic fits are common Blindness loss of speech and hemi or monoplegia may suddenly appear and disappear The underlying pathologic process is obscure Seldom is the diastolic pressure below 130 mm Hg Effective lowering of the blood pressure however achieved results in gratifying improvement

Threatened or minor strokes often repetitive are common In the past they were attributed to occlusion by thrombosis or embolism of the terminal branches of the cerebral

(4) Lancet 2 75 33 Aug 9 1958 [printed: La cet 2 75 33 A g 9 3 7 335 Aug 16 1958]

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Occlusion of the basilar artery results in changes similar to those of carotid occlusion. Average age at onset is higher. The limbs of both sides are usually affected, sometimes at the same time, sometimes successively in a few days. Articulation and swallowing are usually impaired. Severe headache, usually fronto occipital, is common. Onset of obstruction of the basilar artery is usually manifested by a distinct though transient apoplectic seizure; it often recurs and gradually deepens. Massive occlusion is commonly fatal. In many cases basilar insufficiency causes transitory symptoms comparable with those in carotid occlusion. These are due to deficient circulation in structures normally supplied by the pontine and medullary branches and by the posterior cerebral artery on one or both sides. Attacks of dizziness, a feeling of faintness with disturbed balance, tinnitus or momentary loss of speech are common. Numbness on one or both sides of the face or paresthesias referred to one half of the body may occur. Transitory diplopia is common. Most significant are episodes of dimness of vision or blackout.

Treatment of carotid and basilar occlusion is directed toward promoting collateral circulation to minimize the extent of cerebral infarction. Systemic blood pressure and general circulation must be maintained. Injection into the stellate ganglion has been abandoned. Vasodilator drugs such as papaverine and histamine have proved of little worth. The only physiologic vasodilating agents are the products of metabolism, of which carbon dioxide is the most active. Inspiration of 5% carbon dioxide in 95% oxygen for 5 minutes every hour is the most rational way of promoting maximal opening of the collateral circulation. There is a strong hypothetical case for anticoagulant therapy if diagnosis of carotid or basilar occlusion is established, particularly if transitory episodes are occurring. Resection of part of the artery or removal of the clot and re establishment of blood flow should be considered.

Over 75% of proved cases of spontaneous subarachnoid hemorrhage are due to ruptured aneurysms. Mortality is 45-60% with conservative treatment. Cerebral angiography permits certain determination during life of the exact position and nature of the source of hemorrhage. Most cerebral aneurysms arise from derivatives of the carotid arteries and may be grouped as (1) those derived from the carotid artery

from its point of entry into the subarachnoid space to its termination (2) those derived from the anterior cerebral or anterior communicating arteries between the hemispheres and (3) those derived from the middle cerebral arteries in the depth of the sylvian fissures

Active treatment can be logically applied only after an ac curate diagnosis which requires bilateral carotid angiog raphy carried out as soon as possible Direct surgery on the aneurysm or some form of carotid ligation is indicated within 8 weeks of hemorrhage If more than 8 weeks have elapsed since the last hemorrhage conservative treatment is preferable to surgery Perhaps with the use of hypother mia intervention will be possible even sooner

Intracerebral hemorrhage may occur from rupture of an aneurysm buried within the substance of the brain This is common in those arising from the interior or middle cere bral arteries Intracerebral hematomas caused by leaking or ruptured angiomatous malformations develop more slowly and less catastrophically than those due to ruptured aneu rysms Clinical findings are those of a rapidly expanding intracranial lesion in an otherwise healthy person Angiog raphy confirms diagnosis Treatment is surgical evacuation of the clot and excision of the angiomatous malformation if possible at the earliest opportunity Massive intracerebral hemorrhage in patients with diffuse vascular disease and hy pertension is common and usually terminal Selected patients may benefit from surgical evacuation of the intracerebral hematoma

Carotid Artery Murmurs Continuou Murmur over Ca rotid Bulb—New Sign of Carotid Artery Insufficiency is re ported by Lamar E Crevasse and R Bruce Logue[5] (Emory Univ) Obstruction of the carotid artery without occlusion is common and usually unrecognized Clinical manifestations are varied although the classic syndrome of carotid artery thrombosis monocular blindness and contralateral motor and sensory disturbances is well recognized Carotid and basilar arterial insufficiency to the head is probably as com mon as the routine stroke Murmurs associated with carot id artery disease have received little attention The intra cranial systolic bruit over the eyeball represents narrowing of the intracranial portion of the internal carotid at the siphon

(5) J A M A 167 2177 2182 A g 30 1958

and is transmitted and heard best over the ipsilateral eyeball

A systolic murmur may be heard over a partially occluded internal carotid at the angle of the jaw It may be paradoxically present on the side of carotid thrombosis when turbulence of flow through a partially narrowed external carotid is produced by increase in collateral flow around the occluded internal carotid

Routine auscultation of the head and neck has revealed a localized continuous murmur over the partially occluded carotid bulb the commonest site of atheromatous involvement This may be the earliest sign of carotid artery insufficiency The *murmur may herald complete occlusion* of the carotid and irreversible neurologic deficits The murmur is well localized over the carotid bulb transmitted with blood flow up the carotid and is absent or only faint at the base of the neck (the continuous murmur of the aortic arch syndrome is loudest here)

A continuous murmur over a partially occluded artery is due to collateral circulation inadequate to maintain diastolic pressure distal to the partially obstructed segment Both systolic and diastolic pressure gradient is present across the segment Turbulence of flow in both systole and diastole creates a continuous murmur

Incidence of systolic and continuous murmurs in the general hospital population varied from 2 to 7% In an older age group (average age 75 7) 8 of 100 patients had such murmurs and 6 of these had overt neurologic symptoms

This continuous murmur led to early recognition of the syndrome in completely asymptomatic patients with unsuspected carotid artery insufficiency patients in whom diagnosis of cerebral thrombosis was suspected and patients in whom transient neurologic symptoms appeared usually in relation to changes in blood pressure

Carotid artery insufficiency is treatable by surgery and anticoagulant therapy Early recognition and appropriate therapy before complete thrombosis may favorably influence results

Diagnostic Value of Horner s Syndrome in Thrombosis of Carotid Artery is evaluated by Desmond S O Doherty and Joseph B Green[6] (Georgetown Univ) Definitive diagnosis of carotid artery thrombosis is best made by arteriog

(6) N   l gy 8 842 845 N embe 1958

raphy Physical examination has been of little help in this regard except in a few patients in whom ipsilateral optic atrophy or central retinal artery occlusion exists combined with contralateral hemiparesis or sensory loss Palpation of the common carotid artery in the neck or the internal carotid artery in the pharynx has proved unreliable and compression of the common carotid artery on the side opposite the suspected thrombosis may produce syncope Syncope however may also result from this maneuver in basilar artery insufficiency and thrombosis of the anterior cerebral artery

Of 18 patients with carotid artery thrombosis proved by arteriography and surgery ipsilateral Horner s syndrome was observed in 12 whose lesions represented different levels of carotid occlusion Anhidrosis was present in 1 patient who had thrombus in the external and internal carotid arteries None of the others with thrombosis restricted to the internal carotid artery had a sweating disturbance

According to Jaffe and associates the sympathetic fibers concerned with facial perspiration leave the pupillary fibers at the bifurcation of the common carotid artery and follow the external carotid artery and its branches Therefore as would be expected in thrombosis of the internal carotid artery Horner s syndrome was incomplete ptosis and miosis being the prevalent signs In some patients the sympathetic lesion was manifested by a slight difference in pupillary size and a minimal droop of the upper lid These findings are easily missed unless specifically sought during examination repeated observations are often necessary

The cause of the sympathetic disturbance in occlusion of the carotid system is not clear Evidence favors a concept that ischemia of the sympathetic neurons of the third order may occur caused by decreased blood flow through vasa nervorum arising from the carotid artery The transient nature of the eye signs paralleling other signs of carotid insufficiency suggests that the sympathetic disturbance and hemiplegia have similar causes

Ophthalmodynamometry and Intracranial Vascular Disease are considered by Robert W Hollenhorst Bailliart s instrument for measurement of retinal artery pressure is a fairly simple tension spring device calibrated to measure pressures of 10 150 Gm and equipped with a brake for stop

(7) M Cl N rth Am 4 951 959 J ly 1958

ping the plunger at any point for reading By means of this instrument the eyeball is converted into a sphygmomanometer which registers the systolic and diastolic blood pressures of the retinal artery (or more probably those of the ophthalmic artery) according to the identical principles used when the brachial systemic blood pressure is measured with the blood pressure cuff Readings are taken by observing the behavior of the retinal arterioles on the optic disk

The recorded values in the literature for supposedly normal persons are extremely variable According to various authors the diastolic range is from 18 mm to 72 mm Hg and systolic pressures are said to range normally from 36 to 1(0 mm Hg Among patients without ocular or neurologic disease over 90% have essentially equal retinal artery pressures in the two eyes

Measurement of retinal artery pressures by ophthalmodynamometry of patients with intracranial vascular disease is proving to be a valuable aid in diagnosis It was found that 72% of patients with intermittent insufficiency or thrombosis of the carotid artery had lowered retinal artery pressure on the side of the affected carotid artery and slightly elevated pressure on the opposite side With rare exception a difference of pressure of 5 10 mm Hg or more between the two sides is a significant finding caused by interference with the blood flow through the carotid vessels into the ophthalmic artery A lowering of the retinal artery pressure on the wrong side was noted in 5% of patients In 2 this was due to bilateral carotid lesions In 23% of patients pressures on the two sides were equal This finding therefore does not rule out the possibility of carotid involvement because the blood probably is supplied to the ophthalmic artery by the collateral vascular system

Measurement of retinal artery pressure has been found of value in the diagnosis of postural hypotension and it is of interest in the syndromes of intermittent insufficiency or thrombosis of the basilar artery system or of the aortic arch syndrome

Theory and Rationale of Anticoagulant Therapy in Occlusive Cerebral Vascular Disease Long term anticoagulant therapy is generally considered beneficial in arteriosclerotic thrombosis and occlusion of the internal carotid and basilar arteries associated with intermittent ischemic episodes In

cidence of attacks is reduced or abolished but the course of severe infarction is not affected once it has occurred In man improvement is noted within a few days or weeks after instituting anticoagulants

To determine whether anticoagulants improve collateral circulation John S Meyer[8] (Wayne State Univ) occluded the middle cerebral artery in 23 monkeys and 11 cats Half were then treated with heparin or Dicumarol® to maintain clotting time between 40 and 90 minutes and prothrombin time between 40 and 80 seconds To produce severe ischemia or infarction blood pressure was lowered when the middle cerebral artery was occluded During the next 24 hour dye was injected intravenously to study changes in vascular permeability Oxygen tension was measured polarographically

In normal cortex blood flow was rapid Individual blood cells could not be identified Occlusion of the middle cerebral artery in presence of low blood pressure resulted in failure of collateral circulation to compensate Severe circulatory changes appeared in the cortex viz pallor due to collapse of small arterioles and venules pale and cyanotic cortex swelling of the brain with widening of gyri and obliteration of sulci and reduction of oxygen tension to 5 20% of normal

Red blood cells adhered to one another and formed large clumped masses in the veins White blood cells began to adhere to the walls of the venules and further obstruct passage of red cells by narrowing the lumen and hemoconcentration was occurring in the terminal venules These processes continued progressively interfering with blood flow so that segments of red cells moved slower and slower and finally became static Several hours later platelets agglutinated If collateral circulation continued to fail during the next 24-48 hours arterioles and venules became static If collateral circulation returned stasis could be reversed even if present as long as 4 days Carbon particles introduced into areas of vascular occlusion adhered to vessel walls and clumped together in the same manner as did red cells

Administration of heparin or Dicumarol® before vascular occlusion modified these events Flow slowed but not to the same degree Cortical oxygen tension decreased and cyanosis pallor and collapse of small vessels occurred Clumping of red cells and adhesiveness of white cells to vessel walls did

(8) Radiology 70 815 8 4 J 1958

not occur platelets did not agglutinate and platelet thrombi did not form Diapedesis of red cells and perivascular hemorrhage were common but intravenous injection of India ink did not result in agglutination of carbon particles Increase of collateral blood flow produced more rapid resumption of normal flow in ischemic areas than in untreated animals although resulting perivascular hemorrhage might be extensive

Strokes—Diagnosis and Modern Treatment II Treatment Irving S Wright[9] (Cornell Univ) reports that total death rates decreased and development of further emboli was interrupted when anticoagulants were used in cerebral embolism

Of 104 patients with early cerebral thrombosis 53 received anticoagulants and 51 did not Fourteen (27 5%) of the control group and 9 (17%) of the treated group died The difference was explained almost entirely by thromboembolic complications which occurred in the control group No deaths in the treated group were due to subsequent thromboembolic or hemorrhagic complications The only death from hemorrhage thus far in this series occurred in a control patient

Millikan and co workers report that of 94 patients with intermittent insufficiency of the basilar vertebral system attacks ceased promptly in 90 with the institution of anticoagulant therapy Of 107 with irreversible basilar vertebral thrombosis who received anticoagulants 8% died whereas 31 of the controls or 58% died Of 85 with intermittent insufficiency in the carotid system 82 stopped having attacks when given anticoagulant therapy

Studying the effects of long term anticoagulant treatment the author found that during 2 842 patient months without the therapy there were 229 additional thromboembolic complications of which 67 were cerebral During 2 291 patient months with anticoagulant therapy in these same patients 72 thromboembolic complications developed of which 16 were cerebral In 1 311 patient months with interrupted therapy 48 thromboembolic complications developed compared with 15 episodes during 957 patient months of continuous therapy

Most fatal cerebral hemorrhages associated with anti

(9) Mod Concepts Ca d D 8 525 528 May 1959

coagulant therapy occurred in patients with hypertension The level of the blood pressure at which the increased risk becomes prohibitive is still unsettled Too sudden or profound a drop in blood pressure may result in the thrombosis and occlusion of additional cerebral vessels Kidney function may also be affected adversely Therefore caution must be exercised and if the patient has had extreme hypertension for some years it is probably wiser not to try to reach completely normal levels

None of the vasodilating compounds has been found to improve the cerebral blood flow however this has been accomplished by CO_2 inhalation

Stellate ganglion block has proved disappointing and has been generally abandoned Aneurysms and arteriovenous anastomoses when favorably situated can sometimes be successfully attacked surgically

Use of Anticoagulants in Cerebral Thrombosis Previous reports suggest that anticoagulants prevent fleeting ischemic attacks postpone an impending stroke and arrest the progressive downhill course of patients with cerebral thrombosis C Miller Fisher[1] (Harvard Med School) documented his experiences with 58 patients suspected of having cerebral thrombosis treated with anticoagulant drugs and observed during 5 years In each patient the basic lesion involving the cerebral arteries was thought to be cerebral atherosclerosis and superimposed thrombosis This caused ischemia of the brain either temporary or more prolonged and severe enough to cause infarction

Anticoagulants were administered for a few days to 4 years (mean about 6 months) Dicumarol® was usually used for long term therapy and prothrombin activity determined every 7 10 days was maintained at 10 20% of normal When the neurologic deficit was advancing heparin was administered intravenously or subcutaneously

Therapy is relatively useless if begun when the stroke is full blown Efforts should be directed to patients at an earlier stage of the illness Anticoagulant therapy is rational when transient ischemic attacks are recurring more often lasting longer or reversing themselves less completely i e when a neurologic deficit is accumulating Therapy seems indicated

(1) Neurology 8 311 33 May 1958

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(9) Mod. Con epts Ca di a D s 8 5 5 5 9 May 1959

teriosclerotic The saccular aneurysms (66%) were compara ble in every way to those termed congenital aneurysms in earlier studies They occurred as eccentric dilatations vary ing in size from 1 2 mm to several centimeters The aneu rysm wall was not layered normally but consisted of dense fibrous or hyalinized connective tissue The elastica was fragmented or absent The media and adventitia were usually not distinguishable as separate layers within the aneurysm sac At the site of origin the intima was thickened and hya linized the elastic tissue fragmented or absent and the media frayed or compressed Saccular aneurysms associated with arteriosclerosis (20%) were also noted These were similar microscopically to congenital aneurysms except for presence of cholesterol clefts lipid laden phagocytes and traces of cal cium in the deeper intimal layers at the site of origin of the aneurysm and often within the sac itself

The commonest site of occurrence of all aneurysm was the supraclinoid portion of the internal carotid at or distal to the origin of the posterior communicating artery The next most common site was the middle cerebral artery

Among the 113 aneurysms 71% caused death by rupture Half the deaths occurred after initial bleeding and 21% after subsequent hemorrhage None of the 10 fusiform aneurysms bled Of the 23 saccular aneurysms associated with arterio sclero is in 10 there was no fatal hemorrhage whereas in 65 of 74 saccular congenital aneurysms there was bleeding Incidence of bleeding was about twice as high in aneurysms on the carotid arteries compared with that in those on the vertebral arteries Elevated blood pressure in itself did not predispose to rupture of an intracranial aneurysm Of aneu rysms that bled 96% showed subarachnoid hemorrhage in ome combination with subdural intracerebral or intraven tricular bleeding As an isolated event subarachnoid hemor rhage was noted in only 13%

On the basis of this study it appears that about 17% of existing aneurysms remain asymptomatic undiscovered and not responsible for death They are found incidentally at au topsy However if symptoms referable to an intracranial aneurysm develop probability that the patient will die of in tracranial hemorrhage is 71%—4% within 6 hours from on set of initial symptoms 9% within 24 hours 12% in 48 hours 28% by the end of 7 days 61% within 4 weeks 73 % by the 3d

when a stroke is developing stepwise or gradually during hours or days

Transient ischemic episodes are among the earliest manifestations of cerebral thrombosis and are one of the chief criteria for selecting patients suitable for anticoagulant therapy The clinical picture in the carotid system may consist of unilateral weakness or numbness (of the face hand leg or a part thereof on the side opposite the lesion) dysphasia confusion veering monocular blurring of vision or blindness scintillating scotoma headache and possibly focal epileptic seizures Vertebral basilar involvement is indicated by bilateral weakness and/or numbness peripheral cranial nerve involvement dizziness and cerebellar ataxia

No hard and fast rules have been laid down for the period anticoagulant therapy should be maintained In this series it was stopped after 6 months then started again if further trouble occurred In most patients symptoms did not recur even during a 5 year follow up However in 4 symptoms reappeared when the drug was withdrawn after 1 2 years

Results in this series confirm those previously reported i e that anticoagulant therapy abolishes transient ischemic attacks and prevents or postpones a threatening stroke When used in the early stage of a stroke due to cerebral thrombosis the downhill course appears to be satisfactorily arrested and reversed Patient observed both on and off anticoagulants fared better while receiving them Anticoagulant therapy is more beneficial in the earlier stages of cerebral thrombosis than any other treatment presently available and it is relatively safe

Systematic Analysis of Intracranial Aneurysms from Autopsy File of Presbyterian Hospital 1914 56 was undertaken by Edgar M Housepian and J Lawrence Pool (New York) to determine the natural history of this condition and thus allow rational evaluation of recently developed surgical management Among 13 704 autopsies 113 intracranial aneurysms were found Sex ratio was equal Ages ranged from 13 to 91 No intracranial aneurysm was discovered among about 3 000 autopsies in children under age 12 They occurred oftenest in the 4th 5th and 6th decades

Five aneurysms were mycotic 1 syphilitic 10 fusiform and 97 saccular Fusiform aneurysms are usually cla

( ) J Neu op th & Exper Neurol 17 409 4 3 J ly 1958

teriosclerotic The saccular aneurysms (66%) were comparable in every way to those termed congenital aneurysms in earlier studies They occurred as eccentric dilatations varying in size from 1 2 mm to several centimeters The aneurysm wall was not layered normally but consisted of dense fibrous or hyalinized connective tissue The elastica was fragmented or absent The media and adventitia were usually not distinguishable as separate layers within the aneurysm sac At the site of origin the intima was thickened and hyalinized the elastic tissue fragmented or absent and the media frayed or compressed Saccular aneurysms associated with arteriosclerosis (20%) were also noted These were similar microscopically to congenital aneurysms except for presence of cholesterol clefts lipid laden phagocytes and traces of calcium in the deeper intimal layers at the site of origin of the aneurysm and often within the sac itself

The commonest site of occurrence of all aneurysms was the supraclinoid portion of the internal carotid at or distal to the origin of the posterior communicating artery The next most common site was the middle cerebral artery

Among the 113 aneurysms 71% caused death by rupture Half the deaths occurred after initial bleeding and 21% after subsequent hemorrhage None of the 10 fusiform aneurysms bled Of the 23 saccular aneurysms associated with arteriosclerosis in 10 there was no fatal hemorrhage whereas in 65 of 74 saccular congenital aneurysms there was bleeding Incidence of bleeding was about twice as high in aneurysms on the carotid arteries compared with that in those on the vertebral arteries Elevated blood pressure in itself did not predispose to rupture of an intracranial aneurysm Of aneurysms that bled 96% showed subarachnoid hemorrhage in some combination with subdural intracerebral or intraventricular bleeding As an isolated event subarachnoid hemorrhage was noted in only 13%

On the basis of this study it appears that about 17% of existing aneurysms remain asymptomatic undiscovered and not responsible for death They are found incidentally at autopsy However if symptoms referable to an intracranial aneurysm develop probability that the patient will die of intracranial hemorrhage is 71%—4% within 6 hours from onset of initial symptoms 9% within 24 hours 12% in 48 hours 28% by the end of 7 days 61% within 4 weeks 73% by the 3d

when a stroke is developing stepwise or gradually during hours or days

Transient ischemic episodes are among the earliest manifestations of cerebral thrombosis and are one of the chief criteria for selecting patients suitable for anticoagulant therapy The clinical picture in the carotid system may consist of unilateral weakness or numbness (of the face hand leg or a part thereof on the side opposite the lesion) dysphasia confusion veering monocular blurring of vision or blindness scintillating scotoma headache and possibly focal epileptic seizures Vertebral basilar involvement is indicated by bilateral weakness and/or numbness peripheral cranial nerve involvement dizziness and cerebellar ataxia

No hard and fast rules have been laid down for the period anticoagulant therapy should be maintained In this series it was stopped after 6 months then started again if further trouble occurred In most patients symptoms did not recur even during a 5 year follow up However in 4 symptoms reappeared when the drug was withdrawn after 1 2 years

Results in this series confirm those previously reported i e that anticoagulant therapy abolishes transient ischemic attacks and prevents or postpones a threatening stroke When used in the early stage of a stroke due to cerebral thrombosis the downhill course appears to be satisfactorily arrested and reversed Patients observed both on and off anticoagulants fared better while receiving them Anticoagulant therapy is more beneficial in the earlier stages of cerebral thrombosis than any other treatment presently available and it is relatively safe

Systematic Analysis of Intracranial Aneurysms from Autopsy File of Presbyterian Hospital 1914 56 was undertaken by Edgar M Housepian and J Lawrence Pool[2] (New York) to determine the natural history of this condition and thus allow rational evaluation of recently developed surgical management Among 13 704 autopsies 113 intracranial aneurysms were found Sex ratio was equal Ages ranged from 13 to 91 No intracranial aneurysm was discovered among about 3 000 autopsies in children under age 12 They occurred oftenest in the 4th 5th and 6th decades

Five aneurysms were mycotic 1 syphilitic 10 fusiform and 97 saccular Fusiform aneurysms are usually classified as ar

(2) J Ne op th & Exp Neu 1 17 409-4 3 J ly 1958

frequent cause is ruptured aneurysms Blood in the cerebro spinal fluid establishes the diagnosis although it may not appear there for 6 12 hours Signs of meningeal irritation may not become obvious for 12 24 hours but eventually a stiff neck will probably be found Deepening coma with signs of advancing intracranial pressure points to the pres ence of an intracerebral clot An ipsilateral dilated pupil may indicate the side of the hemorrhage The clot must be evacu ated immediately at this point or the patient will die For simple subarachnoid bleeding conservative management for the first 48 hours using bed rest sedation for restlessness and an open airway offers the best prognosis Cerebral an giography should be performed some time within the 1st week Bilateral carotid injections are routine If angiogra phy is negative conservative treatment should be continued for at least 3 weeks Then a vertebral angiogram should be done unless the general condition is poor If it is negative conservative management is continued with absolute bed rest for at least 4 weeks and relative bed rest at home for an other 4 6 weeks

Carotid ligation offers little protection for aneurysms in the middle anterior and anterior communicating cerebral ar teries They can be handled only intracranially During the acute phase mortality and morbidity of surgery is consider ably higher than later in the course

Management of Spontaneous Intracranial Subarachnoid Hemorrhage A rational approach is attempted by H Thomas Ballantine Jr and David M Klein[4] (Massachu setts Gen l Hosp) Onset of subarachnoid hemorrhage is sudden usually with headache stiff neck and altered con sciousness Bloody cerebrospinal fluid usually under in creased pressure is obtained by spinal puncture Onset of cerebral thrombosis and embolism may be similar with sud den neurologic defects headache and coma can occur The first procedure for an exact diagnosis in a case of stroke is careful lumbar puncture using a small caliber needle tak ing only 1 2 ml fluid slowly and not using jugular compres sion

More than 9 of 10 persons with arteriosclerosi and hyper tension die a few hours or days after rupture of a cerebral artery if hemorrhage has extended into the subarachnoid

[4] C cul tio 17 1123 1136 J 1958

month 83% by the end of the 1st year 90% by the end of the 2d year and 96% within 5 years

Problem of Intracranial Aneurysm is reviewed by A J Berman[3] (State College of Medicine New York) The three types are mycotic arteriosclerotic and congenital Most are congenital occurring usually in young persons whose arteries show no sign of arteriosclerosis The saccular formation with a narrow neck precludes their being arteriosclerotic in origin

Symptoms depend on many factors The most important is whether or not the aneurysm has ruptured The most frequent sign of a cerebral aneurysm particularly if unruptured is extraocular palsy Large aneurysms that expand suddenly in the cavernous sinus may produce ipsilateral exophthalmos by obstructing venous drainage from the orbit Saccular aneurysms arising from the intracranial portion of the internal carotid artery are apt to cause symptoms by subarachnoid hemorrhage

Skull x rays may help establish the diagnosis The EEG seldom helps Angiography is most specific Vertebral angiography is rarely performed because it is more dangerous than carotid angiography and little could be done if a lesion were demonstrated

Conservative treatment is justifiable in only a few instances such as bilateral multiple intracranial aneurysms arteriosclerotic saccular aneurysms with minimal symptoms arteriosclerotic aneurysmal dilations without serious local symptoms or patients in whom collateral circulation is inadequate Indirect surgical attack for subclinoid aneurysms consists in ligation of the common or internal carotid in the neck For supraclinoid aneurysms ligation in the neck may protect but it is no cure Aneurysms at the bifurcation of the internal carotid are more difficult to treat If a stalk is present its neck may be clipped However most do not have well defined stalks and the carotid must be ligated For unruptured supraclinoid aneurysms of the internal carotid treatment of choice is surgical exposure of the lesion and clipping of its neck If this is not possible the main trunk should be clipped on each side of the aneurysm in conjunction with carotid ligation

Subarachnoid hemorrhage is a serious problem Its most

(3) Angiology 9 136 153 June 1958

the overdistention of cranial arteries and sustained contrac tion of the neck and scalp muscles Most headaches result from overdistention of the extracranial arteries The pain is vascular in origin in practically all cases In time the fear complex becomes a predisposing factor actually lowering the threshold for pain

In migraine there are three phases to consider whereas in histaminic cephalgia there are only two In migraine the first phase is associated with vasoconstriction (which ac counts for the scotomas and cortical manifestations) and is not accompanied bv pain This phase does not occur in his taminic cephalgia The second phase in migraine is ushered in by vasodilation which is the immediate cause of the pain this phase is common to the two syndromes but develops more promptly in histaminic cephalgia than in migraine The third or edematous phase is associated with pain and is common to both syndromes It is of short duration in his taminic cephalgia but may persist for hours in migraine Nausea vomiting and cortical phenomena are usually absent

Patients with a history suggestive of histaminic cephalgia should have a histamine provocative test preferably by sub cutaneous administration of 0 35 mg histamine base The ob ject of treatment in histaminic cephalgia is to alleviate the pain of the acute attack and to prevent subsequent attacks In a few cases breathing 100% oxygen will alleviate the pain markedly if the attack is mild and if the patient resorts promptly to the use of oxygen An oxygen tank and an ap propriate mask at his bedside are necessary The author pre fers the BLB mask Use of oxygen the moment the attack begins may abort attacks of grades 1 and 2 but is of little or no value in attacks of grades 3 and 4 Severe attacks often can be aborted by intravenous administration of 1 cc dihydro ergotamine (DHE 45) at onset of the attack or shortly thereafter These two procedures mav be combined and often are

Rectal suppositories frequently prevent nocturnal attacks

To prevent future attacks histamine desensitization is the treatment of choice

Cerebral Fat Embolism is discussed by Margaret Ritz mann[6] (Univ of Zurich) The clinical picture of fat embo

(6) Psychiat et neurol 135 301 34 Ap My 1958

space Among those with ruptured aneurysms 15% die within 24 hours 26% within 1 week and 45% within 8 weeks the danger period is 1 3 weeks after the initial episode Of the 55% who survive the first 8 weeks 19% die from late recurrent bleeding within 5 years most of these within 1 year

All subarachnoid hemorrhage is consequent to rupture of a vascular channel releasing blood either directly into the subarachnoid space or secondarily after parenchymal hemorrhage The neurologic defect or death is due to primary destruction of brain tissue by the hydrostatic pressure of the escaping blood and the secondary effects of an intracranial hematoma which acts as a space taking lesion The first phenomenon cannot be altered the second can

Marked displacement of the brain may cause herniation through the tentorium with pressure on and necrosis of the midbrain herniation of the cerebellar tonsils through the foramen magnum produces pressure necrosis of the medulla These complications are manifested by rapidly deepening coma pupillary inequality if there is unilateral temporal lobe herniation bilateral Babinski response episodes of hyperextension rigidity and death Early evacuation of the hematoma is often lifesaving

Recurrent bleeding may be responsible for most of the late mortality If the maximum number of patients with aneurysm is to be saved from fatal recurrent hemorrhage definitive surgery must be performed at the earliest relatively safe time after the first hemorrhage This is the time of the patient s earliest clinical improvement and stabilization Early angiography is an absolute necessity Unless the exact size shape location and nature of the lesion is determined no rational plan can be formulated

The ideal operation for aneurysm is occlusion of the aneurysmal neck by suture or clip excluding the sac from the circulation without disturbing circulatory dynamics This may not be possible and the feeding vessel may have to be clipped on each side of the aneurysm In some cases carotid ligation may be preferable and in some it may be the only procedure possible

Management of Vascular Headache Bayard T Horton[5] (Mayo Clinic) points out that the basic sources of pain are

(5) A g l gy 10 43 56 F bru ry 1959

► The publications concerning the kidney are somewhat paradoxical at present There is a relative paucity of good articles dealing with practical advances in diagnosis and treatment However there are numerous important studies of renal physiology It is to be anticipated that the basic information being acquired to rapidly will soon lead to important practical applications —Ed

Aldosterone Antagonists were investigated by Grant W Liddle[7] (Vanderbilt Univ) Recently new compounds the steroid 17 spirolactones have been developed that block the action of aldosterone at the renal tubular level The effects of spirolactone are opposite to those of aldosterone spirolactones are effective only in presence of aldosterone or biologically similar steroids Administration of spirolactone simulates the abrupt withdrawal of aldosterone in all its effects There is increase in urinary Na^+ Cl^- and volume accompanied usually by slight decrease in urinary K^+ pronounced decrease in urinary H^+ and moderate decrease in urinary NH_4^+ Spirolactone differs from other diuretic agents in that it can block all actions of aldosterone Spirolactone blocks the potassium losing action of aldosterone whereas all other diuretics tend to increase potassium excretion

Patients with cirrhosis nephrosis or congestive heart failure reach the point where they are excreting only small quantities of sodium but large quantities of aldosterone These patients respond to spirolactone with an increase in urinary Na^+ and Cl^- and a decrease in urinary H^+ and NH_4^+ K^+ excretion usually falls slightly Although massive 1 day diuresis in patients treated with spirolactone has never been observed continued treatment over several days can be completely satisfactory Large doses of spirolactone have caused drowsiness and ataxia lasting several hours

Urinary 17 ketosteroid 17 hydroxycorticoid and aldosterone levels are affected little by 1 3 days of treatment with spirolactone It is suggested that spirolactone blocks the action of other steroids at a peripheral site but does not block the secretion of steroids by the adrenal glands With more prolonged treatment it is to be expected that the spirolactone induced sodium loss would intensify the stimulus to aldosterone secretion

(7) A M A Arch I t M d 10 9 3 1004 Dec mbe 1958

lism is due to obstruction of the arterioles or capillaries by crudely dispersed fat contained in the circulating blood Usually the lungs are affected first later other organs among them mainly the brain kidneys and skin The commonest source (91%) of fat embolism is yellow bone marrow Traumatic *lipemia is a normal sequel to bone injury and becomes* of pathologic significance only when associated with other factors

Statistically fat embolism commonly follows fractures There is usually a symptom free interval between the trauma and onset of clinical symptoms lasting from a few minutes to a few days During this time fat is being mobilized from the area of injury and accumulated in the blood In the author s patient *this free interval was always less than 24 hours*

Diagnosis of pulmonary fat embolism is often difficult because of the insidious onset and transition into generalized embolism Generalized fat embolism usually develops within 3 days If it includes the pulmonary circulation the symptoms of generalized involvement appear simultaneously with or follow the pulmonary symptoms If the embolism misses the pulmonary circulation primary cerebral fat embolism will ensue

In cerebral embolism the commonest symptoms are apathy and tiredness which through somnolence and sopor *lead to deep coma Occasionally only milder psychic dys*functions such as lapse in memory disorientation or hallucinations develop The psychic disturbances may outlast the neurologic changes The neurologic findings are usually scant because the patients are often comatose and/or their limbs are immobilized However the pupils are accessible to examination Mydriasis miosis or anisocoria occur with about equal frequency In about half the patients the pupils do not react to light Pyramidal and extrapyramidal involvement is common Most patients present a Babinski sign Monoplegia and hemipareses are less common Involvement of the vegetative *centers may lead to high therapy* resistant fever urinary and rectal incontinence hyperglycemia and glycosuria and dyspnea .

adds additional damage to the already injured renal cellular elements

Signs and Symptoms in Chronic Renal Failure II Vomiting Twitching Hemorrhagic Diathesis Convulsions Itching and Diarrhea were studied in 41 patients by Poul Effersøe[9] (Community Hosp Copenhagen) over several years One or more periods of vomiting occurred in 24 Vomiting was rare at serum creatinine concentrations under 8 mg/100 ml At levels between 8 and 20 mg about a third of the patients vomited and at levels over 20 mg almost all patients vomited Thus renal function proved to influence greatly the incidence of vomiting The height of the blood pressure was unrelated The incidence of vomiting was independent of the type of diet—whether low protein or normal—when no bicarbonate was given Administration of bicarbonate had no influence on the incidence of vomiting when the diet was normal but tended to decrease incidence among patients on a low protein diet Whether or not bicarbonate was given in both high and low protein diets the incidence of vomiting tended to be high with a concurrently high serum total carbon dioxide but this was particularly pronounced if bicarbonate had been given

Incidence of twitching depended on renal function Height of blood pressure had no demonstrable influence Among patients not receiving bicarbonate incidence was the same on a normal and on a low protein diet Incidence of twitching appeared to be raised considerably after administration of bicarbonate

Hemorrhagic diathesis was observed only at serum creatinine concentrations of 14 mg/100 ml or over and only in a small proportion of patients It nearly always manifested itself as epistaxis and all patients died within 2 months of the first hemorrhage Hypertension evidently had no influence on incidence of bleeding

Convulsions occurred in 7 patients In 2 they were definitely and in 2 probably of tetanic origin In these 4 convulsions immediately followed massive bicarbonate treatment usually resulting in a pronounced rise of serum total carbon dioxide So called uremic convulsions in chronic uremia are probably always of hypertensive or tetanic origin Itching was present at one or more periods in 15 patients increasing

(9) Act m d sc di 160 417-430 1958

Perhaps spirolactone will have some value when combined with other diuretics by augmenting the natriuretic effects while diminishing the kaliuretic effects of the latter Possibly spirolactone will have some place as a diagnostic and investigative tool that can be used to show to what extent in a given situation sodium retention and potassium excretion are steroid dependent Perhaps it will have heuristic value in the hands of renal physiologists in their efforts to unravel the mechanisms of renal tubular function

Renal Response to Exercise—Urinary Findings Albuminuria casts and red blood cells often occur in athletes after severe exercise in contact sports and in sports like rowing which are nontraumatic and involve no body contact Edwin P Alyea and Hayner H Parish Jr[8] (Duke Univ) studied athletes involved in intercollegiate matches in track lacrosse crew football and swimming In all these sports between 50 and 80% of the contestants showed albumin casts and red cells in the urine In long distance track all contestants showed albumin The urine that contained much albumin usually was loaded with casts and red blood cells Length or duration of the event was important in determining degree of abnormal findings

Rowing is truly a noncontact sport Of 47 rowers examined before severe exercise all had negative urine specimens after severe exercise 40 had a trace to 1+ albumin 17 had 1 4 red blood cells per high power field and 16 had casts

Previous studies have shown the urine to return to normal within 24-48 hours after discontinuing exercise The cause of the abnormalities is not known Various hypotheses such as shunting of blood away from the kidneys vascular constriction caused by epinephrine damage to the glomerular filtration mechanism and disruption of the basement membrane have been suggested

The fact remains that at least temporarily the kidney is damaged This may leave the tubules weakened or more vulnerable The question arises as to whether anyone who has had definite renal disease should indulge in severe physical exercise Exercise should probably be limited in patients with impaired renal function or a history of acute or chronic parenchymal renal disease Exercise at least temporarily

(8) J A M A 167 807 813 June 14 1958

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(9) Acta med scand 160 417-430 1958

somewhat with decreasing renal function Nearly all had re ceived some drug which may cause itching in persons with no renal disease With discontinuation of the drug itching often subsided Purely endogenous itching caused by im paired renal function is unlikely to exist

Hypertension has no demonstrable influence on incidence of vomiting twitching or hemorrhagic diathesis but in creases incidence of convulsions Vomiting twitching con vulsions and itching may occur when renal function is about 10% of normal Hemorrhages and diarrhea usually do not occur until function is under 5% None of these complica tions occurs in patients with chronic uremia if the sponta neous hemoglobin level is over 75%

Curable Uremias are classified by J Hamburger[1] (Paris) as (1) false uremias (2) functional renal insufficiencies in cluding azotemia due to lack of salt and other electolytic dis turbances and azotemias of circulatory origin and (3) re versible renal changes including acute tubular nephritis early uremia of glomerular nephritis and lipid nephrosis uremias due to urinary infection obstruction of the urinary tract acute infections and septicemia and those due to vari ous renal diseases that are completely or partially reversible

In false uremias nitrogen retention may result from oligu ria which is often aggravated by rigid dieting because insuf ficient food intake tends to destroy tissue i e nitrogen catabolism and formation of endogenous urea and salt re striction also decreases diuresis and excretory function of the kidney Chronic oliguria may result simply from insuf ficient water intake this can be corrected by increasing in gestion of fluid to 1 5 L daily In other instances the cause of oliguria is more obscure incipient hepatic insufficiency or certain endocrine disorders are sometimes incriminated in these patients but in some the cause remains unknown

Azotemias due to lack of salt are of four types loss of sa line with extracellular dehydration lowering of effective os motic pressure with cellular hyperhydration certain states of alkalosis and certain states of potassium deficit Loss of sa line with extracellular dehydration is treated by intravenous perfusion of plasma and administration of isotonic sodium chloride solutions not neglecting re establishment of pres sure equilibrium and diuresis while azotemia returns rapidly

(1) P e méd 66 1345 1348 Aug 16 and 23 1958

to normal In effective osmotic hypotension with cellular hyperhydration strict reduction of water intake associated with suitable supply of concentrated saline solution rapidly transforms the condition in these patients with recovery of diuresis and return of blood nitrogen to normal However serious such uremia appears complete cure is usually effected in a few days without sequelae In alkaloses normal state is re established in a few days by prescription of acidifying chloride such as chloride of ammonium magnesium or even better of potassium if there is also potassium deficit In potassium insufficiency suitable therapeutic upply of this cation is sometimes indispensable for re establishment of saline balance and normal renal function In experimental potassium loss nitrogen retention with microscopic changes in the kidney can be produced

Acute uremia with myocardial infarct may carry blood urea over 1 Gm /L especially when there are associated electrolytic disorders Renal circulatory disturbances caused by shock favor development of lasting serious kidney lesions of the acute tubular nephritis type For this reason solely from the nephrologic viewpoint energetic emergency treatment should be carried out in circulatory collapse and shock

Acute tubular nephritis is manifested by severe anuria which may last for several weeks but if this dangerous phase is overcome the renal lesions tend to repair and cure is generally complete and without sequelae At present the critical period of subacute renal insufficiency can almost always be controlled due to three types of therapy each of which represents an important advance A special diet high in calories rich in carbohydrates and poor in nitrogen aids in reduction of nitrogen catabolism and of increase in blood urea Correction of electrolyte and water balance has been considerably improved and has aided in disappearance of almost all the symptoms of acute uremia Introduction of methods of extrarenal purge offers security hitherto unknown in that it can compensate for functional failure of the kidney for a prolonged period Most important of these methods is the artificial kidney

Prognosis of severe acute glomerular nephritis has also been considerably improved by the same methods used in acute tubular nephritis Early uremia of lipid nephrosis must be differentiated from that which often is slowly progressive

in advanced disease indicating sclerotic lesions and profound and irreversible destruction of the renal parenchyma In this second type ACTH and cortisone are definitely contraindicated whereas in early uremia it may be of spectacular benefit

At least 25% of chronic uremias are caused not by primary change in the renal parenchyma but by mechanical defect in urinary excretion These are amenable to surgical correction provided it is started before secondary renal changes become irreversible

Since the advent of antibiotics curable uremias include those complicating certain serious infections such as interstitial streptococcic nephritis and malignant endocarditis Other uremias are partially reversible such as those that supervene in any renal disease e g renal lithiasis polycystic kidney chronic nephritis renal tuberculosis kidney infarct etc In all such patients diet duly adapted to renal function careful correction of superimposed fluid and electrolyte imbalance and suitable treatment of circulatory failure or hemolysis often result in substantial decrease or even return to normal of blood urea Such treatment does not deal directly with the parenchymatous lesion but rather with the resulting functional insufficiency Nevertheless it should not be underestimated because of the immediate relief it brings to the patient and because it may later facilitate definitive treatment of the renal disease

Anemia Associated with Renal Disease was studied by Michael Kaye[2] (Queen Mary VA Hosp Montreal) with the technical assistance of J Ardeth Hill and Hisako Watanabe Anemia is not a common accompaniment of renal disease because usually the condition will be present without having progressed to the extent of sufficient renal failure to cause azotemia Although there is no direct evidence to incriminate urea as the responsible agent its blood level provides the single most useful guide as to when anemia may be expected and of approximately what severity Even so the variation in hemoglobin between different patients at any level of blood urea nitrogen was considerable The reserve of a person s bone marrow as well as the presence of more than one mechanism for anemia may be of importance In addition if the level of renal failure is changing the hemoglobin

(2) J Lab & Cl M d 5 83 109 J ly 1958

may not keep pace There is often a latent period of several weeks during which time with the blood urea nitrogen rising the hemoglobin will show little change After the blood urea nitrogen may have stabilized or even started to fall the hemoglobin may fall profoundly and not rise again until the urea nitrogen has been normal for a considerable time

The presence of anemia in a given patient with renal disease is of no aid in differential diagnosis of the underlying disease

Unless very severe the anemia of itself carries no special hazard and the prognosis is therefore that of the primary condition namely the renal disease If this is acute e g acute glomerular nephritis because of the favorable tendency for healing or at least remission of this stage of the disease the prognosis can be favorable even if anemia is marked In chronic disease glomerular nephritis and pyelonephritis may be taken as examples Similar levels of blood urea nitrogen and hemoglobin may be seen when the patient first comes under observation yet the patient with glomerular nephritis is likely to die much sooner than the patient with pyelonephritis This is the natural history of the disease irrespective of the degree of anemia

Every patient who has anemia secondary to renal disease will likely show evidence of abnormal iron metabolism A hemolytic process may or may not be present but if it is it will probably be superimposed on the changes in iron metabolism

Nephrogenous Polycythemia Jarl Forssell[3] (Univ of Helsinki) reports 28 cases of polycythemia associated with some type of kidney disorder 22 hypernephroma 4 polycystic kidney 1 fibromyxoma and 1 hydronephrosis According to the classification of Lawrence polycythemia was secondary Hematuria was an important initial symptom and was noted in almost all patients with hypernephroma If polycythemia is noted kidney pathology should be suspected In each patient with polycythemia before nephrectomy polycythemia disappeared after removal of the affected kidney In 1 patient polycythemia developed after nephrectomy

A factor called hemopoetin or erythropoetin which regu

(3) A ta med sc nd 161 169 179 19 8

lates erythropoiesis undoubtedly exists Various forms of anoxia stimulate production of this factor The most recent investigations implicate the kidney in production of erythropoetin The chemical composition of erythropoetin is still disputed The association of polycythemia and kidney pathology would be in accord with the hypothesis that the kidney is the site of erythropoetin production Perhaps nephrectomy influences erythropoetin metabolism and polycythemia is corrected

Emergency Intravenous Pyelogram is often of diagnostic value in patients acutely ill with bizarre flank and abdominal pain Colic from ureteral obstruction may mimic exactly an acute intraperitoneal catastrophe and severe emergencies not related to the urinary tract may present clinically as typical ureteral colic Several such cases are recorded by Benedict R Harrow[4] (Univ of Miami)

As a rule there is no difficulty in differentiating appendicitis from ureteral obstruction However retrocecal appendicitis may present a clinical picture identical with that of right renal colic exhibiting right abdominal and right costovertebral angle pain and tenderness Fever elevated white blood cell count urinary symptoms and microscopic hematuria may occur in both conditions Rebound tenderness usually suggests an acute surgical abdomen but is not pathognomonic An emergency excretory urogram will help establish or eliminate the role of the kidney in the process Other abdominal diseases such as ruptured aneurysm renal trauma infection and hydrops of the gallbladder and diverticulitis may occasionally mimic ureteral colic An emergency excretory urogram would be valuable in these conditions also

The intravenous pyelogram can be done without preparing the patient Rapid preparation is also possible in the absence of dehydration by giving 1 unit of Pitressin® in 0 5 cc sterile saline intramuscularly 35 minutes before injection of the dye If tolerated by the patient compression provides better filling of the upper urinary tract the calyces pelves and ureters

CASE 1 —Man 41 had intense colicky right lower abdominal and right flank pain so severe that he writhed in agony Rebound tenderness was present The urine contained 1 or 2 red blood cells and 5 7 white cells per high power fields The white blood cell count was 12 000 with a shift to the left A K U B x ray study revealed no cal

(4) South M J 51 682-688 Ju 1958

cification An intravenous pyelogram done without preparation demonstrated normal bilateral urinary tracts Emergency abdominal exploration revealed an acutely inflamed retrocecal appendix with gangrenous areas

CASE 2—Woman 32 had pain in the right lower abdomen radiating to the right flank and right anterior costal area with temperature of 101 103 F She had exquisite tenderness and muscle spasm over the lower right abdomen and considerable tenderness in the costovertebral angle A catheterized urine specimen contained 15 20 white blood cells per high power field The surgical consultant scheduled an immediate operation for acute appendicitis A urologic consultant asked for a delay in operation of 2 hours to do an emergency intravenous pyelogram It demonstrated delayed function on the right side with moderate hydronephrosis and a right ureter dilated to a point near the pelvic brim Symptoms subsided with antibacterial therapy and later retrograde pyelograms confirmed the low right ureteral block from extrinsic pressure probably from old pelvic inflammatory disease

Radiologic Findings in Bright s Disease are described by J D Dow[5] Plain x rays of the abdomen will show the size and outline of the kidneys Any kidney under 11 cm or over 15 cm long is suspected of being diseased The renal parenchyma is usually uniform in width local irregularities being abnormal

In pyelography the first film taken about 5 minutes after injection is usually regarded as a rough guide to renal function Poor concentration in absence of obstructive hydronephrosis is an indication of poor function Inequality in function in different areas of the same kidney may be an indication of localized parenchymal disease Structural alterations are often noted in the calyces and less often in the pelvis Calyceal hydronephrosis in absence of obstruction indicates fibrosis in the renal parenchyma distal to an affected calyx

In Bright s disease aortography may be used before nephrectomy to try to show that the contralateral kidney is completely normal to show localized obstruction in a renal artery to indicate the amount of functioning renal tissue in hydronephrosis and rarely to show suspected total or subtotal renal infarction

Presacral air insufflation in Bright s disease is used only to demonstrate the kidneys after repeated attempts to show them by plain x rays have failed Radiology plays no significant part in acute phases of Bright s disease

[5] [illegible] y H p R p 107 454-474 1958

In chronic pyelonephritis both kidneys are small often unequal in size irregular in outline and if the calyceal line is compared with the outline of the kidney it will be observed that the parenchyma is uneven in width Renal function varies The kidneys may be extensively diseased yet show no abnormality detectable by ordinary x rays

In chronic glomerulonephritis the kidneys are small but nearly always equal in size smooth and regular in outline and there is no structural abnormality in the calyces pelves or ureters

In the nephrotic syndrome the kidneys are usually but not invariably enlarged smooth and regular in outline nearly always functioning poorly and if the calyceal line can be identified the parenchyma is observed to be wide and even in depth

Acute Tubular Necrosis in Infancy and Childhood This clinical syndrome is characterized by sudden onset of severe oliguria or anuria followed by retention of excretory products In most cases the lesion is reversible if diagnosis is made early and appropriate management instituted Geoffrey C Robinson and Lei Ching Wong[6] (Univ of British Columbia) review the literature and report a case

Among children nephrotoxic agents account for more than half the reported cases of acute renal failure but a high percentage are of unknown cause Sulfonamide intoxication is a common nephrotoxic agent Over 40% of reported cases have been in children 1-4 the age group with the highest incidence of accidental poisoning and it is interesting that poisoning is the major cause of acute tubular necrosis in the reported cases Mortality is highest among infants under age 1 year

No uniform pattern of initial clinical manifestations was found in reported cases Anuria was the most common presenting symptom In a few it was accompanied by other problems such as vomiting shock convulsions and somnolence Azotemia was reported in all cases In most it steadily increased with the duration of oliguria or anuria In most the CO combining power was reduced markedly Of the 37 patients described 12 died during the acute phase of renal failure most during the stage of oliguria A significant find

(6) A M A J Dis Child 95 417-433 Ap 1 1958

ing was pulmonary or cerebral edema and each had received an excessive amount of fluid during this stage

There is no specific therapy Treatment is based on the assumption that the renal lesion is reversible and that survival depends on avoiding or controlling the physiologic derangements due to the impaired renal function Early recognition is important Occasionally diagnosis is not made until after overhydration has been reached The possibility of acute renal failure must be considered in all circumstances when the known etiologic mechanisms prevail These most commonly are nephrotoxic agents states of severe shock and dehydration and increased blood and tissue destruction In disease due to nephrotoxic agents the poison must be eliminated Gastric lavage or BAL may be indicated In severe shock due to plasma volume depletion the lost fluid should be replaced before the development of oliguria

A long range therapeutic plan should be initiated as soon as diagnosis is established In mild cases simple restriction of water sodium chloride pota sium and protein plus provision of adequate calories as carbohydrate will result in a favorable outcome Most therapeutic results depend on careful assessment of fluid electrolyte nitrogen and caloric balance

The initial body weight should be recorded An initial catheter specimen of urine should be examined immediately for reaction specific gravity albumin and microscopic appearance and a specimen should be obtained for culture Serum chemistry studies should be made No attempt should be made to open up the kidneys by forcing fluids In supplying water intake the amount is calculated from the previous day s urine volume plus the insensible water loss Body weight should gradually fall daily A serum sodium level above 130 mEq /L indicates good control of water balance Endogenous protein catabolism is reduced by administration of dextrose

If water intoxication has occurred all intake may be discontinued allowing loss from skin and lungs to correct the imbalance If symptoms are marked a trial of 50 100 cc of 3% saline may be justified If cardiac failure is present digitalis is indicated Potassium intoxication may be treated by intravenous calcium gluconate hypertonic dextrose and insulin cation exchange resins exchange transfusion peritoneal and intestinal lavage and use of the artificial kidney

Continued observation is important during the diuretic stage with serial notations of daily body weight and daily urine collections Frequent determinations of hemoglobin red blood cell counts serum electrolytes nonprotein nitrogen and CO combining power must be continued Water and electrolyte balance are important during this stage Undernutrition infection severe anemia and delayed healing of wounds present further complications during this stage

Abnormalities Found in Mictiocystourethrographies on Infants and Children K V Parkkulainen and P E Heikel[7] (Univ of Helsinki) analyzed 81 abnormal and 50 normal mictiocystourethrographies (MCU) performed on pediatric urologic patients Sterile 25% water suspension of barium sulphate does not irritate the bladder and thus obviates any local or general anesthesia Besides some radiograms taken during the process of filling the bladder by catheter films are also exposed in lateral projection during the micturition Immediately after voiding a radiogram is taken of the kidney area and bladder to determine a possible residual or reflux contrast If any of these is found another film is exposed after renewed micturition

The commonest abnormalities were vesicoureteral reflux postvoiding residual contrast bladder neck anomalies and bladder trabeculation Of the 53 MCU s revealing abnormality in which both excretory urography and MCU were performed the excretory urography was normal in 25 But even in those 28 cases in which both examinations revealed pathologic conditions the information gained by urography was unsatisfactory or misleading in one third especially in the presence of vesicoureteral reflux In contrast in the 28 cases in which excretory urography was not performed the MCU alone revealed the pathologic state in nearly half the cases Consequently the authors strongly recommend that the MCU be performed as a first x ray examination in the pediatric urologic patient especially if there is recurrent urinary infection and a pathologic amount of residual urine Moreover in half of these cases the MCU films showing vesicoureteral reflux yielded information regarding the bladder and upper urinary tract If no reflux is present excretory urography and instrumental examinations are indicated

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The authors present data on 2 patients with the syndrome One patient was age 8 weeks when chemical investigation of persistent acidosis led to diagnosis Addition of sodium citrate to the dietary intake for 20 months resulted in apparently complete recovery The other patient was age 5½ years when renal calcifications were radiographically visualized Continued alkali therapy corrected the acidosis and had a favorable effect on the physical development of the patient

Experimental Pyelonephritis IV Observations of Infections Resulting from Direct Inoculation of Bacteria in Different Zones of Kidney In a previous report in this series Rocha and co workers described an enhanced susceptibility to Escherichia coli pyelonephritis which resulted from a small mechanical injury in the medulla of the kidney The acute pyogenic infection which developed was restricted to the distribution of those nephrons with collecting tubules passing through the area of injury The evidence suggested that obstruction of urine flow with resultant increased intratubular pressure can alter susceptibility to infection Within the affected area bacteria appear to multiply earlier in the medulla than in the cortex thus pointing to a difference in the capacity of these tissues to support the initiation of bacterial infection In this study the bacteria were inoculated into the blood stream or the bladder urine

In the present study Lawrence R Freedman and Paul B Beeson[9] (Yale Univ) injected bacteria directly into cortex or medulla Infection resulted from the introduction of fewer than 10 bacilli in the medulla whereas 100 000 or more were usually required to establish infection in the cortex The lesion which developed after cortical injection was an abscess localized to the site of inoculation With medullary inoculation the area of infection was wedge shaped including both medulla and cortex and apparently involved all nephrons which drained through the site of medullary injury

A factor which may play an important part in the appar

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ent susceptibility of medullary tissue to infection is that the procedure of medullary puncture obstructs a group of collecting tubules with the formation of a segment of intrarenal hydronephrosis In the presence of obstruction of the entire kidney however there remains a difference between *susceptibility of cortex and medulla to infection* Furthermore when infection becomes established in such a kidney the end result is the same regardless of the site of inoculation a diffuse process *involving* the entire kidney substance

The presence of large numbers of bacteria in the urine did not lead *to infection of kidney substance* except *in the* presence of obstruction

Clinical and Histologic Spectrum of Pyelonephritis George L Schreiner[1] (Georgetown Univ) suggests this classification of pyelonephritis (1) acute chronic healed (2) atrophic or *nonatrophic (3) uni or bilateral (4)* primary or secondary and (5) urogenous or hematogenic Factors that seem to predispose to secondary pyelonephritis are instrumentation internal and external obstruction pregnancy diabetes calculus or nephrocalcinosis congenital anomaly trauma hypo *gamma globulinemia properdin de*ficiency defective general resistance and foci of infection Incidence of false positive urine cultures can be reduced with *midstream* clean catch specimens in preference to catheterized urine Of *396* urine cultures taken *307* were positive The commonest organisms were Staphylococcus *pyogenes* coagulase negative (37%) Escherichia coli (22%) Aerobacter aerogenes (18%) and streptococci (14%)

The earliest histologic lesion is focal inflammatory reaction involving infiltration with polymorphonuclear leukocytes Abscess formation is the progression of focal inflammatory lesions Diffuse interstitial infiltration with leukocytes is a variant that probably signifies rapidity of bacterial invasion or failure of a tissue *localizing mechanism Periglomerular* fibrosis progresses from slight thickening of the parietal layer of Bowman s capsule to marked periglomerular cuffing *and ultimate* glomerular sclerosis and hyalinization This lesion probably accounts for the slow loss of renal function Radial scars are a chronic fibrocytic reaction that seems *to* follow the common distribution of round cell infiltrate that runs in a broad band from the medulla to the cortex Inter

(1) A.M.A A h I t M d 10 3240 July 1958

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All renal calculi except for small asymptomatic stones trapped in calyces and apparently doing no damage should be removed surgically Nonsurgical measures help to bring about spontaneous passage of the small ureteral calculi Demerol® not only relieves the pain but relaxes the tone of the ureteral smooth muscle whereas morphine increases the tone and thus may add to the spasm gripping the stone All the urine should be strained to catch the stone After a calculus has been passed or removed the single most valuable general prophylactic measure against recurrence is to force fluids especially water

stitial fibrocytic reaction is a hallmark of chronic pyelonephritis There is pronounced increase in the normally small amount of interstitial tissue and separation of tubules by edema and fibrocytes Nephrosclerosis is a common accompaniment of pyelonephritis even in young children

Pyelonephritis should be suspected in patients in whom onset of hypertension occurs before age 25 or after age 50 Congestive failure has been the presenting syndrome of many patients with pyelonephritis Pyelonephritis closely mimics pre eclampsia and may be responsible for hypertension albuminuria and accumulation of edema during pregnancy or post partum

Urinary Stone Nature and Treatment were studied by Richard Chute (Boston Univ) Urinary stone does not constitute a disease entity in itself Calculi result from some abnormal condition and being the effect rather than the cause show a fairly high recurrence rate unless the underlying cause is discovered and remedied Calculi composed of calcium phosphate and/or ammonium magnesium phosphate (triple phosphate) and/or calcium carbonate comprise 60% of all stones Some of these are secondary to urea splitting infections and some result from both of these factors Metabolic calcium calculi occur in hyperparathyroidism from vitamin D overdosage in bone disease idiopathically from excessive calcium intake and from excessive immobilization

Calcium oxalate is another common constituent of calculi Many stones are composed solely of calcium oxalate and are the typical small rough ureteral calculi that give such acute colic Often they are solitary and do not recur Secondary stones are those that arise from deposition of the urinary salts chiefly triple phosphates on any foreign body in the urinary tract

Renal calculi give symptoms when they obstruct urine outflow Ureteral calculi are more apt to give symptoms because they usually block passage of the urine down the ureter Bladder stones usually cause little pain and may be symptomless Calculi impacted in the urethra give symptoms of difficulty in urination with a small stream

X ray study is the most important diagnostic procedure in detection of calculi Stones of pure uric acid cast no shadow on the x ray film

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The Digestive System

FRANZ J INGELFINGER, M D

PART V

THE DIGESTIVE SYSTEM

ALIMENTARY TRACT

Pattern of Esophageal Motility in Diffuse Spasm is discussed by Brian Creamer F Edmund Donoghue and Charles F Code[1] (Mayo Clinic and Found) In diffuse spasm immediately after the act of swallowing barium fills and distends the esophagus as in health but as the primary peristaltic wave *reaches the level of the arch of the aorta the lower half* of the esophagus suddenly becomes distorted so that the silhouette of the lower half is puckered into a series of pockets giving it a beaded appearance The column of barium may be completely segmented or the change may be minimal causing only a serration of the outline with some narrowing of the lumen The peristaltic wave may progress through the lower part of the esophagus wiping out the abnormal pattern or it may cease at the upper limit of the abnormality The segmentation often changes rapidly in outline and the barium may be thrust in either direction by the abnormal contractions This picture has been described as curling or corkscrew esophagus and as diffuse spasm of the esophagus Dysphagia and retrosternal pain characteristically intermittent and sometimes resembling cardiac pain may be associated with this abnormal x ray appearance

The authors studied 16 patients in whom x rays revealed diffuse esophageal spasm Most had the characteristic clinical symptoms Further 58 patients were investigated in whom symptoms suggested the diagnosis of diffuse spasm but in whom x rays failed to show the abnormality In both groups the deglutitive pressures in the body of the esophagus were synchronously recorded from three tubes with open tips spaced 5 or 3 cm apart

In patients with diffuse spasm elevated resting pressures were found at the pharyngoesophageal junction and pres

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sure with swallowing was shorter and incidence of simultaneous peaks was less than in patients with x ray evidence of diffuse spasm

Among 23 patients with diffuse spasm to whom Mecholyl® was given the test was unequivocally positive in 1 produced pain or a strictly localized rise of pressure or both in 4 and was negative in the others

The studies indicated that the whole of the affected part of the esophagus contracts simultaneously and that barium is forced into pockets of least resistance or zones of lesser strength One patient had a permanent diverticulum and 1 had multiple small diverticula

► [These studies round out the descriptive picture of diffuse spasm of the esophagus and emphasize its difference from cardiospasm at least as far as the typical case is concerned On the other hand a patient may sometimes be seen with what appears to be an esophageal motor dysfunction verging between *diffuse spasm and cardiospasm In our experience* furthermore the Mecholyl® test produces contractions more pronounced than normal in at least half the patients with symptomatic diffuse spasm

It is generally believed that diffuse spasm of the esophagus is an accentuation of the *curling phenomenon so often seen in elderly persons* but since the exact mechanisms underlying both curling and diffuse spasm are not known the relation between the two is a matter of assumption based on the superficial similarity of the motor phenomena they exhibit —Ed.]

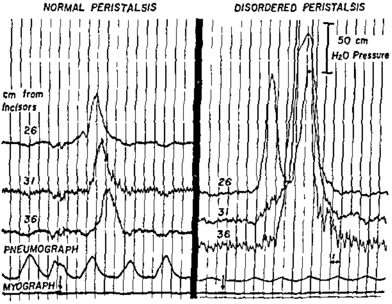
Clinical Test for Esophagitis Differing from previous investigators who used small amounts over short periods Lionel M Bernstein and Lyle A Baker (VA Hosp Hines Ill) gave large amounts of HCl into the esophagus by prolonged continuous infusion Patients were classified as follows (1) those with endoscopic evidence of esophagitis with or without history of esophagitis (2) those with pseudoesophagitis i e those without endoscopic evidence but with clinical history of esophagitis and (3) patients with a normal esophagus without endoscopic evidence or clinical history of esophagitis

TECHNIC —A plastic tube was inserted into the stomach via the nares the gastric contents were aspirated and the tube was then withdrawn until its length from the nares to the tip was 30-35 cm The tube was connected to test solutions in intravenous fluid bottles so placed that changes in solutions could be effected unknown to the subject

Without the patient knowing what solutions were being given 0 9% sodium chloride was administered for a control period of 15 30 minutes at a rate of 100-120 drops/minute As control solutions 5 and 10% glucose were sometimes used After the control period N/10 hydrochloric acid was similarly administered for 30 minutes or until se

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sures in the body of the esophagus were normal However deglutitive pressures were abnormal with normal patterns replaced in the lower two thirds of the esophagus by rises of pressure that were earlier in onset simultaneous instead of sequential repetitive instead of single and of higher pres



Fg 69 – Deglut t e p su e in l we half f e ph gu n h althy p son a d p t ent w th d ffu sp sm N te l of seq ential patt rn in latte Two o tra t ons oc ur d at 26-cm le l th ond f wh cl c d d w th c ntra tion at 31 a d 36 cm P e u e w re l o bnorm lly h gh (C urte y of Cr am r B G stro nt l gy 34 782 796 May 1958)

sure and longer duration than normal (Fig 69) The dimensions of the response varied not only in different patients but also from swallow to swallow in the same patient

The presence of symptoms was associated with a higher incidence of simultaneous responses and with an increase in duration of the deglutitive response in the lower two thirds of the esophagus and this in turn was associated with more frequent repetition of the peaks Only 1 patient had an attack of substernal pain during the test

Among the 58 patients with symptoms but without x ray changes an abnormal pattern of resting and deglutitive pressures was present in 16 but duration of the rise in pres

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vere or typical discomfort was produced The test was considered positive if the test solution elicited pain or burning that was persistent and usually progressive in severity so long as administration of acid was continued Control solutions never produced a positive test

Delivery of acid into the esophagus is accompanied by entrance of the acid into the stomach Symptoms of esophageal irritation were distinguished by (1) pain and burning above the level of the xiphoid (2) rapidity of disappearance of symptoms after cessation of acid administration (3) rapidity of disappearance of symptoms after antacid administration and (4) repetitive production and relief of symptoms

Among 10 patients with esophagitis tested symptoms were reproduced in 8 In 1 distress clearly of esophageal origin was produced although the patient clinically never had such distress The test was negative in the tenth Nine of these 10 patients had x rays but abnormalities were found in only 2 Thus a negative esophagram should not be the basis for disregarding the esophagus as a source of symptoms

Of 12 patients with pseudoesophagitis 10 had a positive test with discomfort localized as it was in the group with endoscopic evidence of esophagitis Dysphagia was noted in only 1 of the 12 patients with pseudoesophagitis contrasted with 4 of the 10 with esophagitis A positive test is simply confirmatory in patients with esophagitis seen endoscopically In patients without endoscopic esophageal abnormality where one might tend to disregard the esophagus as the source of symptoms a positive test is helpful in attributing symptoms to a normal appearing organ

Twenty one patients were tested who had neither history nor esophagoscopic evidence of esophagitis In 20 the test was negative

The test was performed on 7 patients with angina In the 3 with either esophagitis or pseudoesophagitis the test was positive the others had negative tests Cardiac symptoms or ECG changes did not develop during the test Although on occasion esophageal pain may radiate into the arm when both anginal and esophageal pain are present the test will reproduce only the esophageal symptoms

It has been suggested that esophageal pain results from stretching and distortion of nerve endings in the esophageal wall However recordings of intraluminal pressure made at the upper middle and lower thirds of the esophagus during

the control and acid induced pain periods revealed no significant differences in basal pressures. During acid induced pain there was inconstant slowing of propagation of primary peristaltic waves. These observations suggest that esophageal spasm is not the cause of the induced pain.

► [This paper raises two eyebrows one admiring the other dubious. Ever since Chester Jones in his classic monograph on *Digestive Tract Pain* (New York: The Macmillan Company, 1938) described his efforts to reproduce heartburn by instilling acid into the esophagus, the lack of a consistent response to this maneuver has been puzzling. Bernstein and Baker now provide the solution: acid instillation *can* reproduce esophageal distress consistently provided exposure of the esophagus to the irritant is long enough. However, whether the mechanism is one of acid → pain or of acid → muscular spasm → pain is as controversial at present as is the basic mechanism of duodenal ulcer pain.

The dubious eyebrow is directed at pseudoesophagitis, the creation of an entity based merely on the physician's interpretation of symptoms and the patient's response to esophageal acid instillation. Attributing such specificity to the test appears unwarranted and it gets one into trouble. Take the 2 patients said to have angina and pseudoesophagitis. How does one know that a specific set of symptoms is esophageal rather than cardiac in origin? By supporting the clinical impression with the acid instillation test. How is the specificity of the acid instillation test for esophageal symptoms substantiated? By its concordance with the clinical impression. It is circular reasoning.—Ed.]

Jejunal Interposition Operation. Analysis of 33 Clinical Cases is presented by George I. Thomas and K. Alvin Merendino[3] (Univ. of Washington). The esophagogastric junction can be excised and replaced by an interposed jejunal segment. The mucosa of this interposed segment shows greater resistance to acid peptic digestion than the mucosa of the stomach or duodenum. By peristaltic activity the segment prevents regurgitation of peptic juices into the esophagus and thus protects the esophagus from esophagitis. Jejunitis is likewise prevented by this peristaltic action and the isoperistaltic jejunum provides a satisfactory conduit for passage of food into the stomach.

TECHNIC.—A supraumbilical midline incision is extended into the left lateral portion of the chest through the 5th or 6th intercostal space. The 1st or 3d jejunal arteries distal to the ligament of Treitz are short and generally not used. The 3d and 4th jejunal arteries generally run independent of the major vein and are often chosen to supply the transposed segment. The jejunal segment is passed through an aperture in the avascular portion of the transverse mesocolon posterior to the gastric fundus and elevated to the divided esophagus. The length of the interposed segment depends on body build, amount of esophagus resected and anatomic arrangement of the jejunal vasculature, varying between 15 and 48 cm. Any excess jejunum should lie below the diaphragm after diaphragmatic reconstruction. To avoid

3 J.A.M.A. 168:1759-1766, Nov. 29, 1958.

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► [This paper raises two eyebrows one admiring the other dubious Ever since Chester Jones in his classic monograph on *Digestive Tract Pain* (New York The Macmillan Company 1938) described his efforts to reproduce heartburn by instilling acid into the esophagus the lack of a consistent response to this maneuver has been puzzling Bernstein and Baker now provide the solution acid instillation *can* reproduce esophageal distress consistently provided exposure of the esophagus to the irritant is long enough However whether the mechanism is one of acid → pain or of acid → muscular spasm → pain is as controversial at present as is the basic mechanism of duodenal ulcer pain

The dubious eyebrow is directed at pseudoesophagitis the creation of an entity based merely on the physician s interpretation of symptoms and the patient s response to esophageal acid instillation Attributing such specificity to the te t appears unwarranted and it gets one into trouble Take the 2 patients said to have angina and pseudoesophagitis How does one know that a specific set of symptoms is esophageal rather than cardiac in origin? By supporting the clinical impression with the acid instillation test How is the specificity of the acid instillation test for esophageal symptoms substantiated? By its concordance with the clinical impression It is circular reasoning —Ed]

Jejunal Interposition Operation Analysis of 33 Clinical Cases is presented by George I Thomas and K Alvin Merendino[3] (Univ of Washington) The esophagogastric junction can be excised and replaced by an interposed jejunal segment The mucosa of this interposed segment shows greater resistance to acid peptic digestion than the mucosa of the stomach or duodenum By peristaltic activity the segment prevents regurgitation of peptic juices into the esophagus and thus protects the esophagus from esophagitis Jejunitis is likewise prevented by this peristaltic action and the isoperistaltic jejunum provides a satisfactory conduit for passage of food into the stomach

TECHNIC —A supraumbilical midline incision is extended into the left lateral portion of the chest through the 5th or 6th intercostal space The 1st or 3d jejunal arteries distal to the ligament of Treitz are short and generally not used The 3d and 4th jejunal arteries generally run independent of the major vein and are often chosen to supply the transposed segment The jejunal segment is passed through an aperture in the avascular portion of the transverse mesocolon posterior to the gastric fundus and elevated to the divided esophagus The length of the interposed segment depends on body build amount of esophagus resected and anatomic arrangement of the jejunal vasculature varying between 15 and 48 cm Any excess jejunum should lie below the diaphragm after diaphragmatic reconstruction To avoid

(3) J A M A 168 1759 1766 Nov 29 1958

vere or typical discomfort was produced The test was considered positive if the test solution elicited pain or burning that was persistent and usually progressive in severity so long as administration of acid was continued Control solutions never produced a positive test

Delivery of acid into the esophagus is accompanied by entrance of the acid into the stomach Symptoms of esophageal irritation were distinguished by (1) pain and burning above the level of the xiphoid (2) rapidity of disappearance of symptoms after cessation of acid administration (3) rapidity of disappearance of symptoms after antacid administration and (4) repetitive production and relief of symptoms

Among 10 patients with esophagitis tested symptoms were reproduced in 8 In 1 distress clearly of esophageal origin was produced although the patient clinically never had such distress The test was negative in the tenth Nine of these 10 patients had x rays but abnormalities were found in only 2 Thus a negative esophagram should not be the basis for disregarding the esophagus as a source of symptoms

Of 12 patients with pseudoesophagitis 10 had a positive test with discomfort localized as it was in the group with endoscopic evidence of esophagitis Dysphagia was noted in only 1 of the 12 patients with pseudoesophagitis contrasted with 4 of the 10 with esophagitis A positive test is simply confirmatory in patients with esophagitis seen endoscopically In patients without endoscopic esophageal abnormality where one might tend to disregard the esophagus as the source of symptoms a positive test is helpful in attributing symptoms to a normal appearing organ

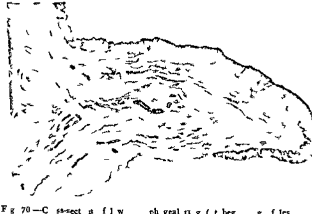
Twenty one patients were tested who had neither history nor esophagoscopic evidence of esophagitis In 20 the test was negative

The test was performed on 7 patients with angina In the 3 with either esophagitis or pseudoesophagitis the test was positive the others had negative tests Cardiac symptoms or ECG changes did not develop during the test Although on occasion esophageal pain may radiate into the arm when both anginal and esophageal pain are present the test will reproduce only the esophageal symptoms

It has been suggested that esophageal pain results from stretching and distortion of nerve endings in the esophageal wall However recordings of intraluminal pressure made at the upper middle and lower thirds of the esophagus during

phagia which occurred only when he ate large pieces of meat X ray study showed a diaphragm like narrowing in the lower end of the esophagus 3 cm above the diaphragm with maximum lumen of 14 mm. After partial gastric resection for unrelated cancer of the antrum he consistently denied having any episodes of dysphagia By x ray study the ring was shown to persist was slightly wider than before and was visible only with maximum di tention of the esophagus After a wasting illness of almost 2 years after the operation the patient died

At autopsy a clear line of separation could not be defined between the unopened stomach and esophagus nor could a lower esophageal ring be palpated with certainty After the specimen was opened a clearly visible nearly transverse thin circular membranous mucosal



F g 70 —C ss-sect n f l w ph geal ri g (t beg g f les rv t on ght s d) N t ph g l m l g upp u f f ee m gi d m li ect on on de fac R t f u der t ce co r d by g tri m Imm d tely be eath muc sa t f m g n b dl f mooth m scl fibe ut t s- ly Co f h lf mad up f o ect t u m scula m d b- m (C rt y f M M hon H E et l N w E gl d J M d 259 1 8 J ly 3 19 8)

shelf was observed between the esophagus and stomach The esophageal ring was covered above by esophageal mucosa and below by ga tric glands The core was composed of connective tissue overgrowth of muscularis mucosae and groups of smooth mu cle fibers apparently *forming an annular band just beneath the epithelial mucosa* that covered the inner free margin of the shelf (Fig 70) In addition mucous glands and excretory ducts as well as blood vessel nerves and lymphatics were present. Although a few lymphocytes were found singly and in minute clusters in the mucosa toward the stomach side there was no suggestion in any part of the lesion of active or healed inflammatory process

Because the anatomic studies showed the ring to represent the junction of the esophagus and stomach and because during life the ring was observed to lie 3 cm above the dia

obstruction it is important to suture the jejunal wall to the edge of the new diaphragmatic hiatus and condition the intraperitoneal arrangement of jejunum by indwelling nasogastric tube Pyloroplasty was also performed

This operation was performed in 33 patients including 20 with peptic esophagitis and 7 with cardiospasm Postoperative complications included suture line leaks in 3 patients electrolyte disturbances in 6 and 4 deaths Follow up on 25 patients revealed late death in 3 patients none related to the operation Weight gain was noted in 17 Normal eating habits returned in 3 9 months Though there was no dysphagia on swallowing solid material many noticed inability to drink fluids rapidly Passage time of food through the jejunal segment was delayed over that of the proximal normal esophagus The dumping syndrome occurred in 13 (52%) patients probably due to the pyloroplasty There were 12 patients who could not vomit

Any doubt concerning ability of the jejunal segment to resist acid peptic digestion has been dispelled by absence of evidence of such pathology Such segments though sequestrated from the small intestine can give rise to afferent pain stimuli when affected by such factors as ulceration There was no evidence of such difficulty in the study patients

► [Esophageal substitution by small and large bowel segments is being widely practiced and extensively reported Even utilization of a completely isolated jejunal segment with the segment revascularized by anastomosis to cervical and facial vessels appears feasible (Ann Surg 149 162 1959) but heterologous aortic and homologous tracheal grafts are unsatisfactory (Am Surgeon 24 521 1958) Most of these procedures are concerned with replacing an organ affected by malignancy In replacing the esophagus stenosed by peptic disease however the additional problem is that of preventing reflux and consequent inflammation of the bridging segment and of the esophageal remnant above it Apparently the length and motility of the interposed jejunal segment achieve this objective.

Another technic is to transpose the ileocolic area with the hope that the ileocecal valve will function to prevent reflux. In dogs however the reflux resistance of the ileocecal valve is less than that of the cardiac sphincter and ileocecal valvular incompetency is a well recognized phenomenon in many normal human subjects (Surgery 44 640 1958)

An interesting complication of jejunal interposition is that of acute gastroduodenal ulceration and perforation observed in 2 children during the early postoperative period (Ann Surg 149 586 1959) —Ed]

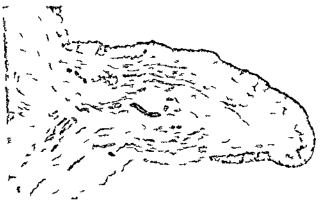
Pathology of Lower Esophageal Ring Report of Case with Autopsy Observed for Nine Years is presented by H Edward MacMahon Richard Schatzki and John E Gary[4] (Mount Auburn Hosp Cambridge Mass)

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(4) N w Engl nd J Med 259 1 8 July 3 1958

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F g 70—C os sect on f l w soph g l ring (at begi g f l curvat o right d) Note soph geal m h g pper f f ee ma gi and m ll sect on undersu face. R st f undersu f ce is co d by g stric m osa. Imme d t y beneath mucos t f m g n bu dl f mooth muscl fiber cut t s v sely Co f h lf m de up f c ect t ue, m sc l ri m sa d ub m osa. (Court y f MacM hon H E *et l* N w E gla d J Med 59 1 8 J ly 3 1958)

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phragm a corresponding piece of stomach must have been herniated through the hiatus If further investigations should show that the ring is always located at the junction of the esophagus and stomach the ring is always associated with hiatus hernia *The long hoped for reliable x ray land mark for the esophagogastric junction in small hiatus her nias will then have been established in patients with rings* Although the ring and physiologic sphincter are located about in the same area they differ in that the sphincter is ac tive and extends over a longer length of esophagus than the ring

► [The original article should be read for its exquisitely lucid description of the structure of a lower esophageal ring and it seems reasonable to assume that *many* of the ringlike narrowings in the distal esophagus are *similarly composed* The statement however that rings of the type de scribed permit radiologic identification of the junction of esophagus and stomach depends on one s concept of this junction. Strictly speaking these rings may permit localization of the junction of gastric and esophageal *mucosa* but does this junction correspond to the gastroesophageal junction in terms of the gross configuration of the two organs and in terms of their muscular characteristics and function? Probably not for gastric mucosa in many apparently normal persons appears to extend upward into a portion of the gut that is tubular and that manifests esophageal motor characteristics In many animals moreover esophageal mucosa extends downward into a round pouch that looks for all the world like stomach *and serves as a food reservoir A first year high school student in biology* would call it stomach but the more sophisticated guided by mucosal characteristics would have to say it was at least half esophagus

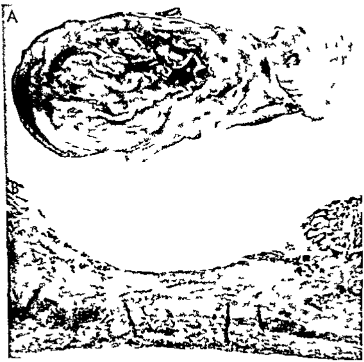
Cases of various esophageal rings are reviewed in the *New England Journal of Medicine (259 378 Aug 21 1958) Rings in the distal esopha* gus are tentatively ascribed to the attachment of the phrenoesophageal ligament by an English author (Brit J Radiol 31 472 1958) but the Boston front is solid in 4 patients operated on at the Massachusetts General Hospital the findings and *conclusions* of MacMahon Schatzki and Gary are roundly supported (Ann. Surg 149 491 1959) Dysphagia in these cases was relieved by excision or digital rupture of the ring com bined with diaphragmatic hernia repair In another instance a ring dis appeared after myotomy and exploration of the lower esophagus (Am Surgeon 25 20 1959) —Ed]

Some Experimental Observations on Gastrointestinal Le sions in *Behaviorally Conditioned Monkeys* are reported by R W Porter J V Brady D Conrad J W Mason R Galambos and D McK Rioch[5] (Walter Reed Army Med Center) Nineteen rhesus monkeys were gently restrained in chairs that provided freedom of all limbs and self feeding fa cilities The chairs were equipped with attachments for pres entation of auditory and visual stimuli automatic delivery of sugar pellet rewards and brief electric shocks and a lever

(5) Psychosom Med 20 379 394 Sept Oct 1958

operated microswitch within easy reach of the monkey All the animals were trained to press the lever for a food reward to avoid electric shock or to adjust to some combination of these events

Although the program for each animal was different the experiments were directed mainly toward a study of emo



F g 71—G (*A*) d m p (*B*) ll t t f d oden l l monk y subject d to h b ha condit oni g p oc d (Co rt y f P rte R. W *t al* Pysch m M d 20 379 394 S pt Oct 1958)

tional behavior In some a conditioned anxiety procedure was used in which a clicking noise occurred for 5 minutes followed by brief painful electric shock when the sugar rewarding lever was pressed In others a conditioned punishment procedure was used in which a shock was administered when the lever was depressed but only in the presence of a warning stimulus (tone or light) In some animals mul

tiple programs were combined in fixed temporal sequences

Of the 19 monkeys 11 died or became moribund after 2 17 weeks of study In each of the 11 animals the most prominent pathologic findings were located in the gastrointestinal tract In 4 extensive hemorrhages and/or erosive lesions of the stomach were noted Five showed well developed duodenal ulcers (Fig 71) In each ulceration had progressed at least through the submucosa into the muscular layer In 1 there was a stellate cicatrix in the duodenum producing pyloric obstruction One showed intussusception in the distal ileum Two that had diarrhea and melena for 2 weeks before death showed areas of hemorrhage and punctate ulceration in the colon with pronounced thickening of the bowel wall in the involved areas

Two pairs of monkeys were studied in a *yoked chair* device so arranged that one animal of each pair (experimental monkey) could delay shocks for both itself and its partner (control animal) by pressing a bar In this way the experimental monkeys were the only ones subjected to the psychologic stress of having to make decisions although both animals in each pair experienced the same physical trauma (restraint and electric shocks) Each experiment was terminated by death of the experimental animals both had duodenal ulcers one with perforation The control animals were killed and found to have normal gastrointestinal organs The 24 hour urinary output of 17 hydroxycorticoids did not change significantly in the animals during the testing period

Five monkeys were confined in the chair restraining device without behavior conditioning They remained normal in every respect during periods of 5 6 weeks Thus restraint alone probably was not the critical precipitating factor in the somatic disorders observed in the experimental animals though it might have played a predisposing role The pathologic changes observed seemed to correlate more with the intensity of the behavior program as a whole rather than any of the specific conditioning technics used

The present study seems significant in that disease processes which are not known to occur spontaneously in monkeys and which show many features characteristic of human disease have been observed in behaviorally stressful experimental situations However proper evaluation of results obtained in any study of psychosomatic relationships with ani

mals is difficult and extrapolation to similar problems in man is hazardous

► [The meaning of the results of the combined conditioning procedures on individual monkeys is not readily apparent. The facts that multiple gastrointestinal lesions were produced (hemorrhages erosions chronic ul eration intussusception and colitis) and that animals subjected to intensive conditioning schedules could not survive for more than 5 days suggest that the stressful stimuli were overwhelming rather than subtle i.e. in terms of human experience they resemble the legendary Chinese torture device of dripping water slowly but incessantly on the forehead rather than mimicking the anxieties and frustrations of everyday life.

The experiments with the paired monkeys whatever their significance, must be appreciated as brilliant and fascinating experimental design The experimental animal of each pair is of course the executive mon key so widely publicized in the lay press and on the face of it here is a real laboratory counterpart of the successful American barking decisions into rows of ever jingling telephones Yet the authors are properly cau tious and suggest that selection criteria and constitutional factors may play a role in the susceptibility of the executive monkey to gastroduodenal ulceration It must also be remembered that the rhesus monkey has a low gastric acid output compared to man his fasting gastric acidity is almost invariably neutral and a pH of 3 is regarded as good acidity in this ani mal Moreover what Webster s *New Internat onal Dict onary* says about this monkey suggests it has been frustrated for many years rhesus —a name given by Audebert (1797) who says it has no meaning —Ed.]

Incidence of Peptic Ulceration in Some African Tribal Groups was studied by Alan B Raper[6] (Kampala Uganda) at autopsies of subjects over age 10 Clinical records suitable for statistical analysis were not available Acute ulcers were not considered Among chronic ulcers the degree of activity was not assessed It was sufficient that a definite crater with macroscopic evidence of fibrosis should be present

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listed as police cases Hospital cases (554) were autopsies on patients dying in a hospital

In onlv 5 patients had peptic ulcer been diagnosed before autopsy These were duodenal ulcers 2 with perforation and 3 with pyloric stenosis Ulcer was the cause of death in 3 of these patients and in 6 others in whom it was undiagnosed during life Among the latter 2 duodenal and 2 gastric ulcers had perforated and 2 duodenal ulcers had caused fatal hemor

RELATIVE INCIDENCE OF GASTRIC AND DUODENAL ULCERS

	Hosp t l Cases		I lce Case	
	M l	F m l	M l	F m le
Exam d	4 4	100	193	29
Total ul rs	6	6	23	0
D od l l rs	66	6	0	0
Gastr l rs	10	0	3	0
D od l / G tric	6 6 / 1		6 7 / 1	

rhage In the whole series of 776 cases 105 peptic ulcers (table) and 5 gastric carcinomas were found

The generally high incidence of peptic ulcer 15 3% in men and 4 65% in women contraverts previous reports from tropical Africa especially autopsy reports and suggests that the causes of peptic ulcer are abundantly operative in tropical Africa but that the conditions in which the disease may be brought to notice are rarely fulfilled For male subjects the gross incidence of peptic ulcer in group A was 20 6% in group B 13 68% and in group N 5 4% These differences do not necessarily suggest variable racial su ceptibility to ulcer more likely they reflect the stresses of a hard life and poor food

► [This is illuminating obviously African tribal groups exposed to Western ways must make decisions The incidence of peptic ulcer in African tribes living by themselves and free of outside influence is however still not known and probably will never be known Perhaps in such an aboriginal society tradition and ceremony will not brook anyone playing executive —Ed]

Relation of Chronic Peptic Ulcer to Coronary Sclerosis was investigated by G Watkinson[7] (Leeds England) in two autopsy surveys which included (1) 13 000 records of

(7) G tr ent l gia 89 292 371 1958

examinations performed in Leeds during 1930 49 and (2) 7 000 examinations performed in 9 towns in England and Scotland in 1956

Among 7 722 autopsies of men in the Leeds survey 1 415 chronic ulcers (18 4%) were found 525 (6 8%) had caused death and 890 were found by chance (11 5%) Twice as many ulcer scars as active ulcers were found incidentally Among 4 918 women examined at the same time 433 ulcers (9 5%) were found 91 (2 6%) had caused death and 342 (6 9%) were found fortuitously Three times as many scars as active ulcers were found by chance

In the National survey among 4 151 autopsies of men 518 (12 4%) chronic ulcers were found 333 (8%) were found incidentally and 185 (4 5%) had caused death Among 2 936 women examined 184 ulcers (6 3%) were found 74 (2 5%) had caused death

Major coronary sclerosis was said to be present when large atheromatous plaques had caused material narrowing of the arterial lumen had become calcified or had caused ischemic complications in the myocardium

Although the over all frequencies of total coronary disease were similar in both surveys about 4 times as many deaths were attributed to coronary infarction in the National as in the Leeds survey the respective figures being 12 9 and 3 3% for men and 8 9 and 1 9% for women

Nonulcer subjects were taken as controls and the expected frequency of coronary disease was computed for each age group and compared with the numbers actually observed Peptic ulcers in men as a whole were associated with coronary disease to a significantly increased degree a change accounted for entirely by duodenal ulcers gastric and combined ulcer had no similar tendency In the Leeds group there were 604 duodenal ulcers in the National survey 166 In the former total coronary disease was observed in 308 (expected in 255) major coronary disease in 166 (expected in 136) and coronary infarction in 28 (expected in 28) In the National survey total coronary disease was observed in 91 (expected 67) major coronary disease in 70 (expected in 19) and coronary infarction in 50 (expected in 24) The differences where present are highly significant P being less than 0 001

Though the association of ulcer and coronary disease was magnified in young and middle aged men dying of chronic

ulcer significantly fewer cases occurred in the elderly reflecting the highly selected nature of the material or some less obvious cause

► [Does anyone ever see a report concerning the co incidence of duodenal ulcer and some other condition with the conclusion that the two disorders are *not* related? Well perhaps in persons with blood group A in active Addison's disease and in pernicious anemia Otherwise however one can find reports of a high degree of association of peptic ulcer with almost anything coronary disease atherosclerosis emphysema tuberculosis gallstones portal cirrhosis central nervous system disease rheumatoid arthritis iatrogenic or spontaneous adrenocortical overactivity hyperparathyroidism hematologic disorders diabetes (see next abstract) smoking *aspirin alcoholism and insecurity I can't understand it where do they* ever find enough people to make up those control groups?—Ed]

Postmortem Analysis of 812 Gastroduodenal Ulcers found in 20 000 Consecutive Autopsies with Emphasis on Associated Endocrine Disease is presented by Edwin H Ellison Jerome S Abrams and Darell J Smith[8] (Ohio State Univ) Incidence of ulcer was 4 1% There were 372 gastric and 3?9 duodenal ulcers The ratio of gastric to duodenal lesions was 1 5 1 in acute and 0 6 1 in chronic lesions Acute ulcers occurred in both stomach and duodenum in 21 patients and chronic ulcers occurred in both locations in 23 The ratio of male to female patients was 2 5 1 in chronic gastric ulcer and 3 5 1 in chronic duodenal ulcer Chronic disease was rare in patients under age 30 but 20% of acute lesions occurred before this age The average age at death of all patients with ulcer was 56 years

About 15% of patients coming to autopsy with chronic ulcer had had some form of gastric surgery 6 months or less before death Death was a direct consequence of acid peptic disease *due to hemorrhage or peritonitis in 48%* of patients with chronic ulcer but only 23% of acute duodenal lesions and 14% of acute gastric lesions In 16% of patients dying before age 20 and 37% dying after age 50 ulcer was the cause of death

Most gastric ulcers acute and chronic were found on the lesser curvature within 5 cm of the pyloric ring (Fig 72) In the duodenum 6% of chronic lesions and 13% of acute lesions occurred distal to the first portion Nearly 1 of 10 patients with gastroduodenal ulcer had associated acid peptic disease of the esophagus

Concomitant central nervous system disease (cerebral edema thrombosis or hemorrhage meningitis tumor but

(8) Am J Surg 97 1 30 Ja[nua]ry 1959

bar poliomyelitis or meningeal hemorrhage) was found in 37% of patients with acute ulcers and 7% of those with chronic ulcers There were 52 cases of pancreatitis most often due to posterior gastroduodenal perforation into the pancreas The incidence of diabetes was 2 5% in the entire group of 20 000 autopsy cases and 4 6% in those with gastro

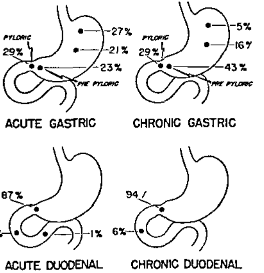


Fig 7 —Loc t f o ul P tb lb ul t w f d 13%
t a d 6% f h (Court y f Ell so E H Am J S g
17 30 J y 19)

duodenal ulcer a statistically significant increase In acute duodenal ulcer the incidence of diabetes was 10 8%

There was a paucity of associated disease in the pituitary thyroid and parathyroids suggesting that dysfunction of these endocrine organs probably plays little or no role in the pathogenesis of peptic ulcer Islet cell abnormality including 3 benign adenomas 2 malignant tumors and 2 examples of extreme hyperplasia was found in 26 patients This supports the suggestion that the non beta islet cells of the pancreas may be significant in patients with intractable acid peptic disease

The incidence of adrenal cortical hyperplasia was 13 2% in the ulcer patient which is twice that seen in the entire group of 20 000 autopsies and equal to or greater than that

reportedly found in hypertension or diabetes This finding gives additional weight to the hypothesis that the adrenal gland is related to gastric secretion and plays an important role in the etiology of acid peptic disease

► [This study shows that the incidence of peptic ulcer as determined by autopsy records of patients dying between 1937 and 1955 and the relative incidence of gastric and duodenal lesions have not changed appreciably from autopsy figures determined in earlier years The number of deaths caused by ulcer in the *chronic* ulcer cases is indeed far higher than that usually considered by the clinician but the figure is not so startling when it is remembered that this is a series of cases selected on the basis of two criteria death and presence of peptic ulcer —Ed]

Peptic Ulcers in Rheumatoid Patients Receiving Corticosteroid Therapy Robert H Freiberger William H Kammerer and Abraham L Rivelis[9] (Cornell Univ) made x ray studies of the upper gastrointestinal tracts of 114 patients with rheumatoid arthritis who had been on corticosteroid therapy for 6 or more months The incidence of peptic ulcer was 31% compared with 9% among patients with rheumatoid arthritis not receiving corticosteroids There were 4 reactivated ulcers There was no sex predilection The incidence of ulcers seemed to depend on the amount of steroids and not on the length of administration Gastrointestinal symptoms were absent or minimal Nevertheless the usual complications did occur Gross bleeding developed in 3 patients acute perforation in 2

Only 5 of 35 ulcers were in the duodenum This is practically the reverse of the ratio for idiopathic ulcer in the general population Roentgen features of the duodenal ulcers were not unusual All but 2 gastric ulcers were in the antrum 8 at the greater and 20 at the lesser curvature Many were *shallow with the diameter of the crater considerably greater* than its depth and surrounded by a zone of smoothly thickened stomach wall Because of this shallowness and because of the absence of rigidity of the stomach wall detection of the ulcer was often difficult No stomach cancer was seen

► [The high incidence of gastric ulcer in patients receiving corticosteroid therapy is deservedly emphasized here —Ed]

Bronchitis Aspirin Smoking and Other Factors in Etiology of Peptic Ulcer A Allibone and F J Flint[1] (Sheffield England) questioned 119 patients with acute gastric or duodenal hemorrhage and 35 with acute gastric or duodenal perforation as to symptoms of gastric disorder chronic bron

(9) Radiology 71 542 547, Oct be 1958
(1) Lancet 179 182 July 26 1958

chitis and acute respiratory infection starting within 4 weeks preceding hospitalization Each patient was also questioned about consumption of aspirin sulfonamides oral antibiotics alcohol cortisone and adrenocorticotropic hormone phenyl butazone and other medicines and tablets during the 2 weeks preceding hospitalization and about any special strain or worry within 4 weeks Control patients were questioned and examined in a similar manner In 95 of 100 patients the cause of hemorrhage was peptic ulceration

The prevalence of acute upper respiratory infection was not significantly higher among patients with hemorrhage or perforation than among controls and the incidence of chronic bronchitis was slightly higher in the non ulcer group This implies that neither acute nor uncomplicated chronic respiratory infection is important in the etiology of gastric hemorrhage or perforation Respiratory infections are an equally common antecedent of other acute surgical emergencies The incidence of aspirin ingestion was similar in study and control groups and aspirin is regarded as a rare cause of bleeding and perforation Among male patients there were 58 cigarette smokers compared with 42 in the control group The probability that this difference was due to chance is less than 1%

► [The reader is warned the position taken in this article as regards aspirin is distinctly in the minority The majority are so impressed by aspirin as a cause of gastrointestinal bleeding that they are even talking of aspirin anemia but with a few notable exceptions the majority opinion is more supported by floods of words than by unequivocal evidence —Ed]

Evaluation of Buffered versus Nonbuffered Acetylsalicylic Acid Max S Sadove and Lester Schwartz (Univ of Illinois) investigated whether addition of buffering agents improves or gives the same or less satisfactory results as acetylsalicylic acid alone in the conditions for which it is commonly prescribed

The material consisted of two kinds of tablet which were grossly identical in physical characteristics Each tablet contained 0 3 Gm acetylsalicylic acid with or without buffering agents The tablets with the buffering agents containing 45 mg aluminum glycinate (dihydroxyaluminum aminoacetate) 100 mg magnesium carbonate and acetylsalicylic acid (Bufferin®) were purchased and repackaged Bulk acetylsalicylic acid was specially pressed so as to be indistinguishable

(2) P tg d Med 24 183 188 A g t 1958

from the other tablet The drugs were packaged in coded bottles labeled A or P Neither physician nor patient knew the identity of the analgesic administered other than by code Placebos were not indicated since the two drugs were studied for comparison only

Half the patients got 2 tablets first from bottle A and half from bottle B The coded compounds were rotated every 24 hours Thus when possible the cross over design was used so that patients with pain persisting more than 24 hours got both tablets and acted as their own controls Studies were conducted on 199 rheumatic and arthritic patients of one hospital and on 155 patients from the medical and surgical services of another

Time of onset degree and duration of pain relief and side effects were noted By these criteria there was no therapeutic difference between the two compounds The incidence of gastrointestinal side effects was 5% for the buffered and 3% for the unbuffered compound Addition of buffering agents to acetylsalicylic acid is thought to serve no useful purpose detectable by clinical or laboratory means presently available regarding analgesic action or tolerance

► [No reason apparently to tell your ulcer patient that he will tolerate Bufferin® better than some other form of aspirin—Ed]

Appraisal of Treatment of Gastric Ulcer Claude E Welch and John F Burke[3] (Harvard Med School) is based on review of records of 367 patients seen between 1952 and 1957 and diagnosed as having benign gastric ulcer Operation was performed on 221 (60 2%) with benign ulcer found in 205 and cancer in 16 (7 2% of operated group) In similar series studied at the same hospital the incidence of malignant ulcers mimicking benign lesions was 14% in 1941 and 10% in 1947 Only 2 gastric cancers are known to have occurred in the 146 medically treated cases a total incidence of known cancer in the present series of 4 9%

Operative mortality in the present series was 3 6% Five year survival of 10 patients treated surgically for ulcer cancer between 1947 and 1953 was 50% These figures when compared to the incidence of cancers masquerading as benign ulcers suggest that the danger of cancer cannot be the sole reason for subjecting all gastric ulcers to surgery in

(3) S g y 44 943 1958

mediately and that some patients may be given a carefully supervised trial of medical therapy

Detection of the ulcer cancer remains difficult of the various diagnostic methods available x ray proved by far the most reliable In 51 cases examined by gastroscopy ulcers were visualized and the diagnoses correct in 23 instances and the question of cancer raised in 6 Cytologic smears in 187 cases were unsatisfactory in 24 and doubtful in 9 Of 148 patients with negative readings 2 had cancer of 6 with positive reports 3 had benign ulcer

The major indications for operative treatment of gastric ulcer are chronic symptoms only partially relieved by medical management gross hemorrhage and failure to heal on an intensive regimen Gastric re ection is the procedure of choice For 4 ulcers located high in the stomach partial proximal gastrectomy was performed in preference to the Madlener procedure in which the ulcer is left in place and distal gastric resection carried out

► [These are not obscure internists writing but distinguished surgeons and Dr Welch s opinion appear to have been sensitive to the changing figures at his own hospital for the incidence of neoplastic ulcer mis diagnosed as benign. Also illuminating are the figures given for the diagnostic accuracy of endoscopy and exfoliative cytology when the results are based on general hospital experience —Ed]

Response to Transfusion as Guide in Management of Upper Gastrointestinal Hemorrhage was studied by Daniel W Elliott Richard Hartle Foster Marshall and Robert M Zollinger[4] (Ohio State Univ) Massive hemorrhage was indicated by an acute episode of bleeding within 6 days of the beginning of therapy with one or more of the following features (1) clinical shock with blood pressure falling below 90 systolic (2) requirement of 3 pt of blood or more in any 24 hours to maintain stable blood pressure and (3) hemoglobin level falling acutely below 9 Gm

Of 279 patients with massive hemorrhage from any upper gastrointestinal lesion except varices or blood dyscrasias 74% initially responded to supportive and transfusion therapy Satisfactory response was predicated on disappearance of external signs of bleeding stabilization of vital signs and if blood was still being given an ensuing appropriate rise in hemoglobin level It must have persisted 24 hours or longer to be called a response If after 24 hours of stability

(4) A M A A h S g 77 386 395 S pt mb 1958

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(3) Surg 44 943 1958

ural reluctance to intervene surgically in these patients

The following factors did not help in predicting response to transfusion therapy history of previous hemorrhage sex or race initial hemoglobin level or rapidity of blood loss be fore treatment began The patient least likely to have a fa vorable response would be aged 50 70 have a gastric ulcer and exhibit shock

When only the patients who eventually responded were considered 71% had shown this response within 24 hours of the beginning of treatment At the end of 48 hours 94% of patients who were going to respond had done so There

OVER ALL RESULTS IN 2/9 ADMISSIONS OF 262 PATIENTS WITH MASSIVE ACUTE UPPER GASTROINTESTINAL HEMORRHAGE 1948 57

	C s	D H	M %t
Emergency operation for uncontrolled hemorrhage	60	9	15
Transfusion therapy including operation for rebleeding or electively	219	21	9 6
Over all results	279	30	10 7

fore there is little to be gained in continuing a trial of trans fusion therapy beyond 48 hours

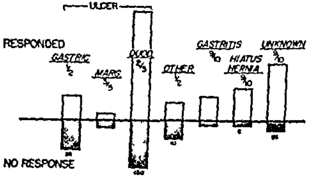
Indications for surgical intervention were failure of re sponse to as many as 5 pt of blood within 24 hours and fail ure of response to any amount of blood after 48 hours of ther apy Rebleeding under treatment was also considered a sur gical indication and this occurred in one fifth of those who initially responded to transfusion therapy

A reasonably respectable over all mortality experience of 10 7% (table) appears to support the concept of treatment by transfusion therapy followed by operation if this fails How ever examination of this experience year by year reveals no apparent trend toward improvement in mortality Delay in surgery could be identified as a causal factor in one third of the total deaths It appears that though the ready avail ability of whole blood makes a trial of transfusion therapy easier and afer it also may contribute to a temptation to postpone decision about operation

Results of Three Methods of Therapy for Massive Gas troduodenal Hemorrhage Statistically Valid Comparison Karl E Karl on Irving F Enquist Clarence Dennis and

subsequent signs of hemorrhage appeared rebleeding was said to have occurred The 72 patients who never achieved any such satisfactory response to transfusion had emergency surgery or bled until they died

No appreciable difference in the incidences of satisfactory response to transfusion was found among the various decades of life except that patients above 70 and those below 30 had a slightly higher incidence of favorable response Particularly in patients over 70 in whom complicating diseases often increase operative risks attempts to control hem



F g 73 —D gnos s r ponse to t sfu on N mbe f pat ents w th b di gn s ep e e t d by ba L ghte port n abov l ne i d at numbe r po d ng to tr nsf s on nd p port r pond ng i d e t d by fra t Othe group ncl de 3 g tr a m m s 3 l my m a d l mpho rcoma ul ated d t cu l m h ma gioma nd duodenal e s on b meta t t c ca ce J ea b (C rte y f Elliott D W *et al* A M A A b Su g 77 386 395 S ptembe 1958)

orrhage with supportive and transfusion therapy appeared distinctly advantageous As many patients responded to transfusion after hematemesis as responded in the whole group However shock was a graver prognostic sign About half those bleeding into shock responded to transfusion

Only slightly less than half the patients bleeding from a gastric ulcer re ponded to transfusion whereas among those bleeding from duodenal ulcer almost as many responded as in the average for the whole group Only when bleeding arose from acute gastritis hiatus hernia or in the absence of demonstrable pathology could a good response to transfusion be expected in each of these conditions 1 in 10 patients failed to re pond (Fig 73) In 49 of 55 patients in whom no pathologic changes could be demonstrated transfusions elicited good response This appears to substantiate a nat-

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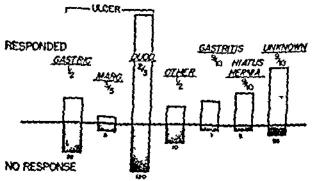


Fig 73 —Diagn s r pons to t ansfu n Numb r of pat e t w th ch d agnosi r rep es ted by ba L ghter port o abo e l n nd te number re pond ng t tr fu n and p p rt n r spond g s ind at d by t act Oth g p cl d s 3 gast a c omy 3 1 myom d l mphosa com ulce t d d rt ru hum h m ng ma nd duoden l e o on by m t t te cance l e ch (Co rtesy of E l ott D W et al A M A A h Su g 77 386 395 Septembe 1958)

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and if over 500 ml is required every 8 hours to maintain normal blood pressure and pulse operation is undertaken Mortality in each group was 14% (Table 1) sources of bleeding are given in Table 2

In patients who have lost at least 40% of the calculated normal total circulating red cell mass surgical therapy offers a salvage rate not significantly different from that of medical therapy for the bleeding episode However patients treated nonoperatively may again be subjected to the same risk from subsequent massive hemorrhage Selection of patients for therapy of massive bleeding on the basis of loss of

TABLE 2—Bleeding Sources in Therapy Group

	Group 1	Group 2	Group 3	Total
Duodenal ulcer	19	21	17	57
(astric ulcer	5	10	7	22
Gastric cancer	2	2	1	5
(astritis	1	2	2	5
Hiatus hernia	4	—	—	4
No lesion at operation	1	1	—	2
Esophageal varices	1	—	—	1
Leiomyosarcoma jejunum	1	—	—	1
No lesion by x ray	14	—	5	19
Undetermined	10	1	3	14

40% of the calculated normal total circulating red cell mass is extremely useful No patient who lost less than 40% of the calculated normal total circulating red blood cell mass died of exsanguinating hemorrhage

Experience with the nonoperative regimen in elderly patients indicates that risk of nonoperative management in selected patients may not be as high as anticipated Therefore the selective operative regimen is suggested for elderly patients

► [The meat of the 2 articles ab tracted above is that upper gastrointestinal hemo rl age even if cirrl otics with bleeding esophageal varices are excluded continues to be attended by a con iderable mortality which is not reducible by rigorous plans of treatment whether they i clude early or late ope ative attack hero c attempts at tran fu ion robust or sickly diet drugs or no drugs This i not only discourag ng but suggests that we houl l pay mo e attention to the lonely voices cry ng that our u e of t sfu ons in treat ng upper gastro ntestinal hemorrhage i all too ready and hast ly incons derate

Obv ously new method are needed to combat bleed ng from esophagus

Sidney Fierst[5] (Brooklyn) treated 130 patients with massive gastroduodenal bleeding according to one of three methods chosen at random nonoperative regimen (group 1) immediately operative regimen (group 2) and selective operative regimen (group 3) All had an acute bleeding episode within 7 days of hospitalization sufficient to reduce their total circulating red blood cell mass to below 60% of normal or red cell count to below 2 500 000/cu mm

The nonoperative regimen is based on the concept that hypovolemia and hypotension prevent the clot from being

TABLE 1—MORTALITY IN THERAPY GROUPS

Sub-Group	No of Pts	Deaths	Mortality
1 Nonoperative	58	8	14%
2 Immediate operation	37	5	14%
3 Selective operation	35	5	14%
Total	130	18	14%

11% m rt l ty p t t wh ctually am t pe t n (O d d b f p t n)

dislodged from the bleeding vessel that a quiet stomach assists in keeping the clot in place and that low gastric acidity prevents the clot from being digested Therefore strict bed rest reassurance and frequent feedings of antacid milk gelatin mixture are the basis of treatment Blood is given only for air hunger and evidences of cerebral or myocardial hypoxemia or for blood pressure below 80 mm Hg systolic and then in 250 cc amounts only

Under the immediately operative regimen transfusion is immediately given and operation is performed as soon as the blood pressure and pulse are normal

According to the selectively operative regimen all patients over age 50 and all with clinical evidence of arteriosclerosis are operated on as soon as possible after the transfusion and restoration of blood pressure and pulse to near normal levels (within 12 hours) Patients under age 50 and without arteriosclerosis or history of previous hemorrhage are transfused with 1 500 ml blood as soon as possible It this restores blood pressure and pulse to normal the transfusion is continued

(5) An S g 148 594 60 O t b 1958

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Obviously new methods are needed to combat bleeding from esophagus

stomach and duodenum Is cooling off the angry stomach the answer? See following article —Ed]

Depressant Action of Local Gastric Hypothermia on Gastric Digestion Use in Control of Massive Hematemesis Owen H Wangensteen Harlan D Root Peter A Salmon and Ward O Griffen Jr[6] (Univ of Minnesota) found that gastric cooling considerably retarded gastric digestion Observations with use of systemic cooling were made on fish frogs toads and rats and observations with local gastric cooling were made in dogs and man Digestion of small frogs



Fig 74 — Digestion of 3 small spring frogs kept for 6 hours in stomachs of bullfrogs shows marked difference in degree At 24 C spring frog was about 50% digested at 15 C it was about 20% digested and at 2 C frog was still alive At 2-4 C small frogs have survived up to 20 hours within bullfrog stomach (Courtesy of Wangensteen O H et al J A M A 169 1601 1608 Apr 4 1959)

in the stomachs of bullfrogs kept at 20 C was essentially complete in 24 hours When the temperature was maintained at 2 C the small frog was still alive after 11 hours or more (Fig 74) dead but intact at 24 hours and only slightly digested at the end of a week

Local gastric hypothermia was achieved in man and the dog by circulating 150 200 ml /minute of a cooling solution (equal parts ethyl alcohol and ice cold water) through an intragastric balloon Constant intragastric balloon temperature of 10 14 C and circulating volume were maintained by a hypothermia machine In man the rate of digestion of a 2 Gm meat bolus contained in a gauze sack was measured under gastric normothermic and hypothermic conditions The weight loss of the bolus after 4 hour averaged 55% in

(6) J A M A 169 1601 1608 Apr 4 1959

normothermic stomachs and 18% in persons subjected to gastric cooling

The mean reduction in volume of gastric secretion during periods of gastric hypothermia was 80% in man and 90% in the dog Total free acid and total pepsin production were also markedly reduced

Re ults of these experiments suggested that massive gas tric hemorrhage might be controlled by use of local gastric cooling Before insertion of the intragastric balloon the pa tient s stomach was evacuated of all clots by nasogastric tube or by lavage with an Fwald tube An empty balloon was wrapped around the end of an 18 F double lumen tube and passed into the stomach The free end of the tube was con nected to the hypothermia machine and the coolant was in troduced into the balloon During circulation of the cooling solution through the balloon the patient s temperature was recorded constantly Although the systemic temperature usually remained normal external heat was applied as a pre cautionary measure A small nasogastric tube also was in serted beside the balloon into the stomach to evacuate blood as it appeared in the stomach and as an aid in evaluating continuance or cessation of bleeding

Nine patients with massive hemorrhage from duodenal ulcers and 1 with active bleeding from a gastric ulcer were cooled successfully with cessation of hemorrhage and with out recourse to operation Cessation of bleeding occurred in 2 of 3 patients with massive hemorrhage from esophageal varices and bleeding was slowed in the third patient Gastric cooling has been carried out in man up to 125 hours without apparent ill effects

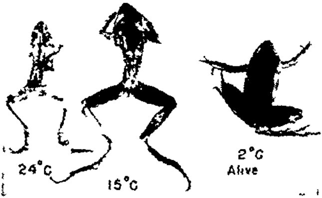
In miscellaneous conditions causing hematemesis includ ing gastric and breast cancers with thrombocytopenia gas tric erosions due to uremia steroid ulcers and gastric hemor rhage in early convalescence from other surgical procedures results were variable Local gastric cooling is however of promising therapeutic value in managing massive hematem esis from peptic ulcer linked conditions of duodenum stom ach and esophagus

Results of Adequate Gastrectomy with Gastroduodenos tomy S Arthur Localio and William Dwyer[7] (New York Univ Postgrad Med School) present a follow up study on

(7) S g Gy ec & Obst 108 207 210 F bru ry 1959

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F g 74 —D g t n of 3 m ll pr ng f g k pt fo 6 h u n st m hs f b ll f g show m k d d ff r nc n deg ee At 24 C pr ng fr g wa bout 50% d g st d at 15 C t w about 20% d g t d and at 2 C f og wa st ll l At 2 4 C m ll fr g ha e urv d up t 20 h u w th n bullf g tom h (C urt sy f W ngenst n O H *et al* J A M A 169 1601 1608 Ap 4 1959)

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of Surgeons[8] Data were obtained from 29 hospitals in 15 communities with populations ranging from 15 000 to 1 000 000 A consecutive series of patients was obtained from hospital records or some equally reliable source starting in 1957 and working backward until 100 cases were compiled or the beginning of 1950 was reached whichever occurred first Fifteen hospitals reported 100 or more operations Excluded were such condition as gastric or jejunal ulcer and hypertrophic pyloric stenosis An operative fatality was any death occurring within 30 days of operation

There were 432 surgeons who performed 2 562 elective operations About 80% of the patients had gastric resection In about 30% of all procedures including both drainage procedures and resections vagotomy was also performed The over all mortality for all procedures was 4 3% (110 deaths) for resections 4 9% and for drainage procedures 1 7% The range in mortality in individual hospitals was 0 7 8% 9 hospitals had death rates of 6% or greater and 11 hospitals had rates of 3% or less

Resection removing 50 75% of the stomach was the most popular The extent of the resection had little effect on mortality For the Billroth I reconstruction the mortality was 2 8% for the Billroth II 5 1% Vagotomy accompanied only 18% of all gastric resections However it was performed in 78% of the small resections

The cause of about half of the 102 deaths for which data were furnished appeared to be directly related to the operation and included such complications as peritonitis hemorrhage and shock The other half of the deaths were ascribed to complications not directly related to the operation itself such as myocardial infarct and pneumonia

No relation could be shown between death rate and size of hospital size of community type of staff or proportion of operations performed by unqualified surgeons or by residents in training but data concerning these factors were incomplete The most likely explanation for a relatively high mortality seems to be the intrinsic risk in gastric resection performed for duodenal ulcer

► [The mortality for subtotal gastrectomy with or without vagotomy is about three times that of a drainage procedure plus vagotomy Subtotal gastrectomy or hemigastrectomy with vagotomy is more effective in preventing recurrent ulcers than drainage procedures with vagotomy Which

(8) Am J S g 96 365 369 S pt mbe 1958

116 patients who had two thirds to three quarters gastrectomy with gastroduodenostomy for peptic ulcer Follow up was 12 months or more in 92% 25 months or more in 63% and 36 60 months in 36% Seven patients died during the follow up none of these had manifested evidence of recurrent ulcer

After surgery 48% of the patients failed to regain their preoperative weight and 60% failed to reach their usual weight All with intercurrent disease capable of adversely affecting weight were excluded from the analysis Mild symptoms of dumping were present in 35% of the patients These did not have to lie flat or take medication to obtain relief In 11% moderate symptoms of dumping occurred daily and occasionally forced the patient to lie down for relief None had symptoms severe enough to cause distress after practically every meal and force the patient to lie down at least once every day Eight (6%) patients had proved recurrent ulcers at or near the gastroduodenostomy all 8 were in the group of 71 patients who had had resection for duodenal ulcer The recurrence rate in this group was 11% No patient treated for gastric ulcer had a recurrence Two thirds to three quarters gastrectomy with gastroduodenostomy though a safe procedure (there was only 1 postoperative death in the entire group) is associated with significant incidence of postoperative nutritional and dumping problems The operation is considered a failure in patients with duodenal ulcer because of the high rate of recurrent ulcer but continued trial of the procedure for gastric ulcer is justified

► [*Follow up studies on the results of a specific surgical procedure for the treatment of peptic ulcer are a dime a dozen Why then is this paper abstracted In the first place Dr Localio set up a purposeful study he created a group of patients subjected to a technically homogeneous gastrectomy with the express intent of discovering the results Secondly the follow up was conducted by his associate Dr Dwyer who had no part in the surgery an excellent precaution employed in few other surgical follow up studies Finally the conclusions are unequivocal the authors are dissatisfied with the Billroth I type of anastomosis in the surgical treatment of duodenal ulcer The weight of the evidence is thus turning against Dr Henry N Harkins and his Seattle group the group in the United States that has argued most eloquently for using gastroduodenostomy in treating duodenal ulcer surgically*—Ed]

Elective Operations Performed for Duodenal Ulcer with Their Mortality Results of Survey in Selected Ohio Hospitals by Survey Committee Ohio Chapter American College

II gastrojejunal anastomosis was performed at the initial admission or during the 5 year study period on 62 patients 14 of whom underwent gastrectomy primarily for reasons other than gastrointestinal hemorrhage No recurrent bleeding episodes occurred during the follow up period in these 14 patients Of the 48 patients operated on primarily for bleeding 10 had recurrent gastrointestinal hemorrhage within 5 years Of the 10 patients in whom recurrent hemorrhage took place within 5 years of gastrectomy 6 were among 12 who underwent emergency gastrectomy for uncontrolled bleeding

Gastrointestinal hemorrhage was fatal in 8 (5 9%) of 136 patients

The serious prognostic import of bleeding as a complication of duodenal ulcer and the inadequacy of over all management in coping with this problem are emphasized by the fact that only one third of the patients escaped all the following events within 5 years subtotal gastrectomy recurrent hemorrhage and death Hemorrhage following gastrectomy appears to be prevalent in those operated on because of bleeding

► [The recurrent opinion (see 1957 58 YEAR BOOK p 520) that the results of subtotal gastrectomy undertaken for bleeding duodenal ulcer are plagued by a high rate of recurrent bleeding is not only disturbing but also puzzling What is there about a bleeding ulcer patient that makes him susceptible to renewed bleeding after operation even though the recurrent ulcer is at a totally different site from the original one? Certainly no bleeding tendency in this type of patient has ever been described —Ed]

Late Prognosis after Partial Gastrectomy for Ulcer Follow up Study of 361 Patients Operated on from 1905 to 1933 Urban Krause[1] (Univ of Uppsala) conducted a 23 50 year follow up study on patients who underwent Billroth II operations Two thirds to three fourths of the stomach was usually resected Patients who died immediately or during the first months after operation and those who died of carcinoma of the stomach within 5 years of operation were excluded from the study Follow up rate was 94%

Over all mortality was 210 whereas that to be expected was 163 1 This difference is statistically highly significant The cause of death was stomach cancer in 28 reliably substantiated in 25 The cancers developed an average of 24 3 years after surgery The difference between the 25

(1) [illegible] 114 341 354 1958

consideration should influence the surgeon most when he undertakes elective surgical treatment of duodenal ulcer? For Dr George Crile Jr the answer is clear In the treatment of duodenal ulcer the survival of the patient is the most important consideration (A M A Arch Surg 77 857 1958) —Ed]

Five Year Follow up Study of Patients with Bleeding Duodenal Ulcer with and without Surgery was conducted by Robert M Donaldson Juanita Handy and Solomon Papper[9] (Boston) There were 136 study patients who had one or more of the following black stools that reacted with guaiac hematemesis observed by medical personnel and gastric aspirate that appeared bloody on gross inspection and reacted with guaiac Before onset of gastrointestinal hemorrhage 22 patients had no abdominal pain or other symptoms referable to the gastrointestinal tract Seventy eight had typical epigastric peptic ulcer pain and atypical symptoms were described by 36

Of 100 patients first seen during the initial episode of gastrointestinal bleeding 38 had recurrent hemorrhage within 5 years of the initial episode Of these 10 bled on more than 1 occasion Eleven patients died within 5 years of the first bleeding episode 2 were patients with uncontrolled hemorrhage which developed 5 days and 2 months respectively after gastrectomy performed during the first bleeding episode Five years after the initial bleeding episode there were 37 patients who had had neither gastrectomy nor recurrent hemorrhage

Thirty six patients when first seen gave a history of one or more previous episodes of gastrointestinal bleeding Further episodes of bleeding occurred in 15 patients within 5 years of the hemorrhage for which they were first seen At the end of the 5 years 10 of the 36 had had neither subtotal gastrectomy nor recurrent hemorrhage Of 104 patients who lived 5 years from the time they were first seen 49 had bled again and 36 underwent subsequent subtotal gastrectomy

There was no constant pattern of bleeding in the given patient A mild bleeding episode on one occasion was often followed by a severe hemorrhage The reverse also occurred frequently The bleeding episodes *in the study patients did not fall into any clear seasonal pattern*

Subtotal gastric resection combined with an anterior or posterior Polya or Hofmeister modification of the Billroth

(9) New England J Med 259 201 207 July 31 1958

weeks Anterior and posterior fields were used on alternate days The patient was treated in standing position and field size usually was not larger than 10×10 cm Localization of portals over the gastric stump is highly important

In 18 of 19 patients who could be examined after treatment the free acid titer was well below the level present before irradiation Achlorhydria or pronounced hypochlorhydria was present in over half of the patients up to 2 years after treatment

In 12 of the 18 patients who had demonstrable ulcer craters x ray studies showed healing of the ulcer after treatment In 2 others the crater disappeared only after a second course of irradiation 2 reported that they were symptom free 1½ and 8 years after therapy but follow up could not be made and in 2 craters were found 3 years after treatment As the last 2 had been symptom free the ulcers found on re examination may have been recurrences after initial healing

Of the 5 patients who had no demonstrable crater before irradiation therapy in 3 achlorhydria was produced and no symptoms were present 8-15 months after treatment achlorhydria was not achieved and further hemorrhages occurred until a second course of irradiation was given and in 1 a second course of treatment was given because of persistent acid secretion and some distress

Of 17 patients who had pain before treatment this symptom was relieved in 14 by irradiation 2 others were relieved from pain after a second course of treatment

Follow up has been less than 2 years in 16 patients 11 of whom are symptom free and show no evidence of recurrence 1 had recurrent or persistent crater 1 had hemorrhage 1 had pain and 2 died of intercurrent disease Of 7 patients followed 2-8 years 4 have remained symptom free and 3 have had recurrent hemorrhage pain and crater formation

No important side effects were observed even in patients given two or three course of roentgen therapy There was no evidence of injury to other organs in the treated area

► [Theoretically the idea of using radiation therapy to control gastric acidity when physician and patient are both discouraged by ulcer recurring after intensive medical and surgical management is an appealing concept The actual results unfortunately are not striking Ordinarily vagotomy rather than x radiation would appear to be the procedure of choice in treating a patient who has stomal ulceration following simple subtotal

cancer deaths and the expected rate of 11 3 is statistically significant

Pulmonary tuberculosis caused 24 deaths The expected death rate for tuberculosis was 8 7 There were 9 suicides against an expected incidence of 2 The excessive mortality from this cause was *confined* to males Suicides were distributed almost equally between the gastric and duodenal ulcer patients

Among the 151 patients who lived jejunal peptic ulcer developed in 9 men and 3 women Only 2 had been operated on for gastric ulcer

More than 30% of the men operated on for ulcer had a hemoglobin level below 70% whereas this level was recorded in only 1 7% of a control group of hernia patients Blood values in gastrectomized persons should be examined regularly

A history of postcibal symptoms (weakness sweating etc) was obtained in 12 5% *of moderate symptoms in* 1 5% None had severe complaints of this type This low incidence of postgastrectomy complaints may be explained by the long interval (23 50 years) elapsing between operation and follow up study

► [A 94% successful follow up over a period ranging from one quarter to one half a century is a remarkable accomplishment Unfortunately a detailed breakdown as to the number of gastric and duodenal ulcer in the series is not provided Hence the significance of recurrent jejunal ulceration of cancer in the gastric stump and of the high suicide rate i difficult to apply to theories that hold that gastric and duodenal ulcer are etiologically different disorders —Ed]

Radiation Therapy for Stoma Ulcer Occurring after **Subtotal Gastrectomy** Preliminary report of results in 23 patients is presented by Everett D Kiefer and Magnus I Smedal (Lahey Clinic) In 18 patients an ulcer crater was shown by x ray examination whereas in 5 the only objective evidence of ulcer was hemorrhage Seven had had resection for stomach ulcer and 4 had had vagotomy Before roentgen treatment free acidity in the gastric remnant was 20 degrees or over in 12 patients *with demonstrable crater* and 40 degrees or over in 5 *In the 5 patients without demonstrable crater* free acidity was 20 degree or over in 2 Histamine or Ewald s meal were used as secretory stimulants

The tissue dose of x rays was about 1 800 r in all instances The plan of treatment was to give 180 r 5 times weekly for 2

( ) J A M A 169 447-451 J n 31 19 9

Conversion of gastrojejunostomy to gastroduodenostomy did not alter incidence of symptoms or of cardiovascular responses The preoperative glucose meals used in this study did not produce any cardiovascular response that would allow correlation with dumping symptoms later In view of the ECG findings it would be of interest to relate the cardiographic response to posture before operation to the later incidence of dumping

► [The mechanism of the dumping syndrome continues to be hotly debated and to cover our ignorance the fancy phrase homeostatic over reaction has been proposed (Gastroenterology 36 423 1959) Despite the intensive study few attempts have been made to detect the potential dumper *before* gastric surgery by preoperative assay of various mechanisms believed responsible for dumping symptoms An unsuccessful attempt was made in this study but had the authors introduced their preoperative glucose meal intraduodenally rather than by mouth more meaning might have pertained to their results —Ed]

Influence of Secretory Function of Stomach on Nutrition in the Dog Ivan D A Johnston and Richard B Welbourn[4] (Queen s Univ Belfast) with the technical assistance of H O Nevin J Tansey F A Mullan and M Pountain studied in 20 dogs the effects of gastric secretion on nutrition by eliminating the stomach as a reservoir while retaining it as an organ of internal or external secretion The dogs weighing from 8 to 15 kg were separated into four groups group 1 comprised the normal controls group 2 had esophagoduodenostomy with total gastrectomy group 3 had esophagoduodenostomy with the stomach left in situ whereas group 4 had *esophagoduodenostomy with a total gastric pouch* the same as in group 3 except that the external secretion was drained to the exterior Any internal secretion could still enter the circulation

All the dogs lost weight after operation Those in group 3 in which the gastric juice entered the duodenum retained 75% or more of the preoperative weight those in group 2 retained only 50 60% and those in group 4 retained only about 55 65% of the preoperative weight Weight loss was most rapid in the first 3-4 weeks after operation

All the animals operated on excreted more fat and nitrogen in the feces than did the controls Excretion was greatest in those that had total gastrectomy and least in those whose gastric secretions flowed into the duodenum Dogs with total gastric pouches and those without stomachs ex

(4) Brit J S g 46 163 169 S ptembe 1958

gastrectomy On the other hand once both partial gastrectomy and adequate vagotomy have failed to contain peptic ulcer disease radiation therapy might well be considered —Ed]

Cardiovascular Changes in Postgastrectomy Syndrome H L Duthie W T Irvine and J W Kerr[3] (Glasgow Scotland) carried out investigations preoperatively in 10 patients with peptic ulcer in 17 after partial gastrectomy of the Polya type in 4 before and after conversion from Polya to Billroth I gastrectomy and in 5 after gastrojejunostomy The patients were studied in sitting position after a 12 hour fast For 1 hour before and 1 hour after oral intake of 100 ml of 50% glucose the pulse rate blood pressure and ECG recordings were done at frequent intervals and hemoglobin packed cell volume blood sugar and serum potassium estimations were done every 15 minutes Plasma volume estimations were made by determining a change in the disappearance rate from the peripheral blood of human serum albumin tagged with radioactive iodine

Patients with epigastric fullness associated with vasomotor symptoms after the glucose meal were considered dumpers No abnormal cardiovascular response was observed in preoperative studies Reduction in plasma volume occurred in all after gastrectomy and gastroenterostomy but no correlation was found between the size of the shift and presence or absence of symptoms Blood sugar determinations after the glucose meal revealed no difference between dumpers and nondumpers Serum potassium was not low during the period of symptoms

The ECG changes occurred in most patients during symptoms and tended to fall within a similar pattern with lowering and flattening of the T wave sagging of the S T interval and peaking of the P wave In most instances the ECG was again normal within 1 hour after the test meal Repeat studies were done on 5 patients who showed obvious changes after the glucose meal These were given 0 5 mg ergotamine tartrate intravenously after the ECG changes were established In each the ECG changes disappeared within a few minutes after administration of the drug The ECG alterations noted were more in keeping with sympathetic stimulation than with potassium depletion The ability of ergotamine tartrate to abolish the abnormal changes supports this view

(3) B t J S g 46 350 357 J u y 1959

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(4)—Br J S g 46 163 169 S ptembe 1958

creted similar amounts of fat This loss was probably sufficient to account for the weight loss during the period when the animals were eating normal quantities of food

In group 3 barium meals showed that food was swallowed normally After the food entered the duodenum however the greater part of each bolus was regurgitated into the esophagus In none was there any sign of retrograde passage of food into the stomach

It is suggested that the gastric juice plays a part in preserving body weight probably by aiding absorption and thus preventing abnormal losses of food derivatives in the feces The reservoir function is necessary to preserve completely normal nutrition

► [Although the dumping syndrome has stimulated the greatest interest and study other postgastrectomy complaints may be even more mysterious and disabling In particular patients who suffer from severe weight loss malabsorption and diarrhea present a serious problem Some argue that this absorptive defect arises because food moves down the intestine ahead of pancreatic and biliary juices and thus escape adequate digestion According to this report however more subtle mechanisms may explain malabsorption and diarrhea following partial gastrectomy —Ed]

Experimental Atrophic Gastritis Associated with Inhibition of Parietal Cells William O Smith Walter Joel and Stewart Wolf[5] (Oklahoma City) prepared a material which had a potent inhibitory effect on acid secretion of Heidenhain pouch dogs when injected intravenously 1 mg/kg body weight The material consisted of dialyzed lyophilized human gastric content collected from healthy subjects after an overnight fast and reconstituted in isotonic saline

Of 7 dogs given injections of the material 3 died of other causes and 4 received 1 or more intravenous injections weekly for 4 weeks or longer In each dog the effect of the inhibitor gradually became more lasting Autopsies were done at various intervals up to 10 weeks after establishment of complete achlorhydria

There was gross evidence of atrophic gastritis in all 4 dogs The effect was greater in the stomach than in the pouch (Fig 75) Microscopically the stomachs showed disruption of the normal linear arrangement of the cells composing the branched glands marked decrease in the number of parietal cells to the point of disappearance in some instances and a decrease in thickness of the mucosa with increased density

(5) Tr A Am Phys ans 71 30 311 1958

and fibrosis Microscopic changes were less severe in the pouches

The mechanism of the changes observed could not be de termined from the data The significance of the changes also is not clear but the authors point out that the changes are *strikingly similar to those seen in atrophic gastritis* which



F g 5 — St m h 1 H d h n po h f d g g m h pl t f p p t f pooled f g g t tent f m healthy h m bject G tri f ld m k dly fl ed d d m hed mbe t m h w h l ttl ff ct on po ch (Court y f Sm th W O s l T A Am Phy 71 306 311 1958)

often accompanies and may precede development of gastric cancer

► [A report from Dr Wolfs group in June 1959 ind cated that the atrophic changes produced in the stomach by injections of d alyzed and lyophilyzed normal human gastric juice can be elicited consistently in dogs but not in rats that dense fibrosi replaces the parietal cells at the end of 6 months and that a slow return to normal is possible after injections are stopped What does it mean with respect to the pathogenesis of gastritis and cancer? May the results be appl ed to a new treatment of acid peptic d sorders? Since the denervated Heidenhain pouch is much less affected by the injections does the vagus play a permissive role?—Ed]

X Ray Studies on Gastric Micromucosal Patterns The limitations and significance of the micromucosal relief tech nic are evaluated by its originator W Frik[6] (Univ of Er langen Germany) By this method the fine reticulated pat

(6) F rtsch G b R tgen t hl n 88 546-557 M y 1958

tern of the sulci between the areae gastricae may be demonstrated (Fig 76) in 50 60% of examinations failures being ascribable to obesity tense abdominal muscles and insufficient or excessive compression A proper degree of compression is difficult to achieve because the micro relief is not



Fg 76 D tal d m s l fac m g w th pt m l p e (C rt y f F k W Γ t h G b R tg t hl 88 546 557 M y 19 8)

readily appreciated on fluoroscopy even with the aid of an image intensifier

The following micro relief patterns were observed (1) the micro relief pattern with regularly located round to oval areae gastricae of 0 5 1 5 mm diameter (2) medium areae of 1 5 2 5 mm diameter round or polygonal shaped (3) the granular micro relief pattern with the same sized areae as in (2) but with deeper and wider sulci (4) the coarse irregular micro pattern with irregular areae of more than 3 mm diameter

The micro relief pattern cannot definitely indicate

whether the gastric mucosa is histologically normal but cases with normal mucosa tend to have micro relief patterns of types 1 and 2 The coarse irregular pattern suggests atrophic gastritis for it is commonly found in groups with a high incidence of biopsy proved atrophic gastritis i e patients over 50 or those with hypo or anacidity Functional factors may also influence the micro relief pattern When disease exists e g cancer the technic may be useful in identifying the lesion

Radioiodinated Triolein Test for Steatorrhea Morton I Grossman and Paul H Jordan Jr[7] (Los Angeles) studied the level of radioactivity in blood and feces after administration of 0 05 0 2 ml radioiodinated triolein containing 25 50 μc radioactivity The study was carried out in normal subjects and in patients with steatorrhea associated with chronic pancreatitis Radioactivity of blood samples was expressed as per cent administered dose per liter Radioactivity of stool samples was expressed as per cent administered dose contained in the *72* hour collection Total fecal lipid content was determined chemically

Since the correlation coefficient between body weight and blood radioactivity was statistically insignificant blood concentration of radioactivity rather than total circulating radioactivity was used The addition of 30 or 60 ml vegetable oil to the test dose of radioiodinated triolein did not significantly alter the blood or fecal levels of radioactivity At 6 and 9 hours after the test dose there were no differences in blood levels with and without vegetable oil Preliminary administration of Lugol s solution did not alter blood or fecal levels of radioactivity Radioactivity of whole blood was found to be as efficient as or more efficient than radioactivity of plasma or plasma lipid fraction for discriminating between normal subjects and those with steatorrhea

Fourteen patients had chronic pancreatitis with steatorrhea as determined chemically All also had abnormally high fecal excretion of radioactivity but only 4 had diagnostically low levels of blood radioactivity Of the remaining 10 none individually had diagnostically low blood values but as a group they could be statistically distinguished from normal subjects It is felt that a normal blood level of radioactivity does not exclude steatorrhea

(7) G t oent l gy 34 89 900 M y 1958

Site of Absorption of Vitamin B_1 in Man was investigated by C C Booth and D L Mollin[8] Four patients about to undergo *abdominal surgery were given 1 μg of radioactive* B_1 by mouth in 2 100 mg intrinsic factor was also given Three hours later during laparotomy no radioactivity was detected by an end window Geiger Muller counter in the proximal small bowel practically all the activity being in the distal half Plasma radioactivity measured simultaneously was negligible at this time but achieved a peak in 8-12 hours indicating operation did not interfere with absorption

Radioactive vitamin B_1 (1 μg) was *given orally to 12 patients who had undergone resection or short circuiting* of the small intestine and the amount of the dose excreted in the feces was determined Absorption of the vitamin was normal (more than 0 28 μg) in 1 patient who had 8 ft of jejunum resected and in 2 with only 1 ft of ileum resected or by passed In the other 9 patients all with ileal resections or short circuits absorption was subnormal In 1 patient with anastomotic *stricture following resection of 1 ft of ileum* and the right half of the colon absorption returned to normal after 4 days of chlortetracycline treatment

Seven of the patients who had had ileal resections or by passes had subnormal levels of vitamin B_1 in the serum and 3 of these had megaloblastic anemia In those with anemia parenteral vitamin B_{12} or 40 mg /day folic acid orally evoked excellent hematologic response

Vitamin B_1 is absorbed in the ileum of man not in the proximal small intestine This explains why the amount of B_1 which can be absorbed through the intrinsic factor mechanism is strictly limited It also suggests that patients who have had resections or short circuiting of the ileum should be treated prophylactically with this vitamin

► [Cooke impressed by the low serum vitamin B level in patients with ileal resection or disease (Lancet 1 901 May 4 1957) has postulated that vitamin B is absorbed principally in the lower small bowel of man On the face of it this is peculiar business why should a water soluble substance escape significant absorption in the duodenum and jejunum—unless the intrinsic factor binding mechanism ignores usual absorptive patterns Previous studies have suggested moreover that as is to be expected the entire small bowel absorb the vitamin quite efficiently (J Lab & Clin Med 50 667 1957)

In view of the ostensible implausibility of Cooke s views the work here abstracted apparently substantiating them is of great interest Clo e examination however shows that the validity of the conclusions is im

(8) La cet 1 18 1 J n 3 19 9

paired by interpretative problems that beset so many alleged tests of absorption The fact for example that little radioactivity is found in the upper small bowel and much in the lower small bowel 3 hours after the ingestion of vitamin B at a time when little serum radioactivity can be detected is taken to mean that vitamin B absorption is entirely up to the distal small intestine Since radioactivity of intraluminal contents as well as gut wall were measured however another explanation is that at the time of measurement unabsorbed B could be detected where it would be i e in the ileum and that jejunal wall concentrations of the vitamin and serum levels were not increased sufficiently by the absorption that had taken place Studies in the rat as a matter of fact have shown that the wall of the upper half of the small intestine contains considerable vitamin B 2 hours after administration of the vitamin but relatively little at 3 hours In contrast the fourth quarter of the small bowel wall in this animal showed minimal levels of vitamin B at all times whereas the luminal content was relatively huge (Clin Sc 16 663 1958)

The authors would of course argue that negligible serum levels 3 hours after administration of the test dose exclude significant absorption but serum levels are about as treacherous indexes of absorption as can be utilized Does the high vitamin B serum level of the patient with liver disease (J Lab & Clin Med 49 910 1957) for example prove that these patients have increased absorptive capacities? Urinary excretion tests are somewhat more useful but also reflect mechanisms other than absorption affecting the state of vitamin B in the body Even fecal excretion tests of radioactive labeled vitamin B employed after the substance is given by mouth may have to be interpreted with caution in view of the suggestion that vitamin B is excreted in the bile and subject to enterohepatic circulation (Proc Soc Exper Biol & Med 97 780 1958) —Ed.]

Folic Acid Excretion Test in Steatorrhea Syndrome E V Cox M J Meynell W T Cooke and R Gaddie[9] (Birmingham England) carried out the test on 20 normal subjects and on 23 hospital patients who had various diseases such as idiopathic steatorrhea regional ileitis pancreatic disease enterocolitis treated pernicious anemia postgastrectomy anemia and cirrhosis of the liver Diagnosis in those with idiopathic steatorrhea was made by abnormal small bowel x ray patterns and by fecal fat excretion over 6 Gm /day

METHOD—Each subject was given an intramuscular injection of 5 mg folic acid and 48 hours later a similar oral dose After each dose the urine was collected for 24 hours in a brown bottle containing 0 2 Gm sodium bicarbonate and toluene An aliquot of each specimen (about 30 cc) was stored at 0 C until it was assayed for folic acid activity The urine content of folic acid was assayed microbiologically with Streptococcus faecalis NCTC 8123 according to Teply and Elvehjem

In addition to the absolute amounts of folic acid excreted results were expressed as the ratio of the amount excreted after oral administration to the amount excreted after intramuscular injection multiplied by 100 which equaled the excretion index Mean folic acid excretions of the normal sub

(9) G t oe t 1ngs 35 390 397 O be 1958

jects were 2 62 mg after intramuscular injection and 2 48 mg after oral administration Mean excretion index was 95 *Below 70* was considered abnormal In the steatorrhea group mean excretion after intramuscular injection was 2 35 mg whereas mean excretion after oral administration was 0 48 mg The index was 19

Among 22 patients with regional ileitis 6 had abnormal excretion indexes and 4 of these had duodenal or jejunal involvement The others with normal excretion had lesions confined to the lower ileum of these 10 had low serum vitamin b_1 levels and 13 had steatorrhea

In the other groups among those with postgastrectomy steatorrhea 2 showed abnormally low folic acid excretions after intramuscular administration This may have been caused by tissue unsaturation but in general urinary excretion after intramuscular administration of folic acid is unsatisfactory for determining folic acid deficiency Patients with pancreatogenous steatorrhea had normal absorption indexes

In idiopathic steatorrhea 19 of 20 patients had evidence of folic acid malabsorption and in this group only was the mean statistically different from the mean absorption value obtained in other diseases The degree of the defect was not related to the amount of fat present in the feces as even those who had improved *on* a gluten free diet still had abnormal indexes

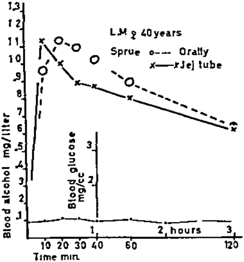
The test is recommended as valuable in the diagnosis and study of patients suffering steatorrhea particularly in those with idiopathic steatorrhea and since folic acid appears to be absorbed chiefly in the upper small bowel in those with diffuse disease involving the duodenum and jejunum

► [As the reader may have noted I deplore as highly inaccurate so-called absorption tests that depend on an orally administered test substance and subsequent measurement of blood levels of that substance Tests that measure the urinary output of an agent previously given by mouth suffer *from similar defects although they may be less influenced by the rate of absorption* i e the urine usually being collected after a considerable time interval the amount of the test substance found in the urine is not as influenced as are serum levels by the speed with which the test material leaves the stomach or enters the blood from the small bowel

The folic acid test as here described has the advantage that the amount excreted after an oral test dose is compared with the amount excreted after an *intramuscular dose and thus factors other than absorption that determine the rate of folic acid metabolism and excretion are to some extent controlled* On the other hand dependency on a microbiologic technic may somewhat limit the practicability of the procedure

Particularly noteworthy is the interpretation of the authors that folic acid, as opposed to vitamin B (see preceding abstract) is ab orbed in the upper small bowel. It is also noteworthy that the test remains abnormal in the face of a remission induced in idiopathic steatorrhea by means of a gluten free diet and that it permits differentiation between malabsorption produced by enterogenous and pancreatogenous mechanisms—Ed.]

Alcohol Absorption in Idiopathic Steatorrhea was investigated by Harald A Salvesen and Andreas Kolberg[1] (Riks hosp Oslo) in 6 patients aged 31 51 The alcohol (96%) was given by jejunal tube to fasting individuals at the rate of 1



F g 77—Blood lcoh l d gl se ry patient 40 w th pru ympt m f 1½ yea vol m ou stool (p to 800 Gm.) f t et on 30 Gm day hypoc l em l ght ema p oth mb n and p econ rtin values 86% weight, 52 3 kg h ght 170 m (C rte y f Sal esen H A d K lbe g A. Acta med sca di 161 135 142 19 8)

ml /kg body weight in 5% solution The resulting blood level curves were compared with those obtained by oral administration of 1 ml /kg body weight of 96% alcohol in 10% solution and also with oral glucose tolerance curves

In 2 healthy controls almost identical results were obtained With intestinal administration of alcohol the curves were steeper reaching maximum (1 3 mg /L) after 10 minutes whereas the oral curves rose more slowly to lower maximum after 25 30 minutes

The oral glucose tolerance curves were flat in all patients

(1) A ta med sca d 156 135 14 1958

With respect to alcohol however the curves of 5 patients revealed rates of absorption and maximums only slightly different from those found in the controls In 1 patient (Fig 77) oral and intestinal curves had the same maximum In the sixth patient absorption rates appeared impaired Thus it seems that patients with idiopathic steatorrhea usually have a normal ability to absorb alcohol

The liver is supposed to do most of the combustion of the alcohol but there seemed to be no differences from the normal in the fall of the curves that would indicate slower combustion in patients with steatorrhea

It appears that alcoholic drinks may be of value in the feeding of emaciated and undernourished steatorrhea patients

Place of Oats in Celiac Diet A Lindsay C Moulton* (Univ of Birmingham) carried out continuous fat balance studies on 4 children with celiac disease who were fed 20-40 Gm fat/day with a diet gluten free except for its content of oat flakes Consumption of 46 and 70 Gm oat flakes daily for 45 and 96 days respectively caused no rise in fat excretion However increases up to 7 day mean values of 4 and 4 1 Gm fecal fat/day resulted when 169 and 163 Gm oat flakes were eaten daily for 22 and 23 days respectively

Barley wheat and rye are considered harmful to celiac children In the case of wheat the prolamine or gliadin is thought to be responsible It is therefore of interest that in a list of the quantities of prolamines in several cereals in which total protein contents are about equal Brohult and Sandegren give wheat rye and barley prolamines as 40 50% 30 50% and 35 45% respectively of total protein and oats as only 10 15% Prolamine content of maize i 50 55% of total protein Although cornstarch like wheatstarch is harmless to the celiac patient the maize prolamine zein does not appear to have been tested and may therefore be injurious Prolamine content of rice is low and rice can be safely eaten by celiac children

Except for maize the various cereal prolamine contents when placed in order of magnitude correspond to a series of foods arranged by van de Kamer and Weijers In this latter series rice maize oat flakes oats barley flour rye flour wheat flour and gliadin are arranged according to their amide nonamide nitrogen ratios which are 11 11 12 13

( ) Arch D Childhood 34 51 53 F b y 195-

14 17 23 and 30 respectively Thus without suggesting a precise quantitative relationship between either of these sets of figures and the effect of the foods on the celiac patients it is obvious that should the prolamine be responsible for the deleterious effect much greater quantities of oats than wheat could be eaten with safety by celiac children Results of the present study give some indication of the intake of oat flakes that the celiac child can tolerate without increase in fat excretion

Intestinal Malabsorption Following Temporary Occlusion of Superior Mesenteric Artery was studied by R A

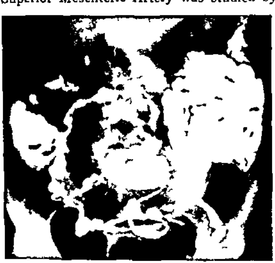


Fig 78 —X r y f m ll bow l h w g b rmal blon l k patt rn w h pool g f ba m (Co rt y f Josk R A et l Am. J Med. 449 455 Septembe 1958)

Joske Munir H Shamma a and G D Drummey[3] (Harvard Med School) in 2 patients

Case 1 —Woman aged 52 had rheumatic heart disea e with auricular fibrillation The sequence of event trongly suggested that a mal absorption syn lrome followed temporary obstruction of the superior mesenteric artery that lasted 34 hours from onset of pain to successful mesenteric embolectomy Re-establi hment of circulation into the superior mesenteric artery was hown directly at econd laparotomy and later by aortography Gross intestinal malabsorption was noted 2 weeks after the ischemic episode and persisted for 3 months The radiologic changes observed in the small bowel on three occasions post

(3) Am J Med 25 449-455 Sept mbe 19 8

operatively resembled those known to result from small bowel infarction However the changes were diffuse rather than segmental and *corresponded well with distribution of the superior mesenteric artery* (Fig 78)

The absorption defect produced was multiple involving fat carbohydrates and protein as well as vitamin B_1 though the different nutrients were affected in varying degree The patient s stools contained 10 15% of a fat intake ranging from 84 to 142 Gm /day There was little if any effect on serum electrolyte levels

CASE 2 —In man aged 54 *malabsorption also followed temporary* occlusion of the intestinal arterial supply lasting about 12 hours The arterial occlusion was due to thrombosis and affected the celiac *axis and superior and inferior mesenteric arteries The thrombus was* removed and a second operation 2 days later demonstrated a viable gut In the 2 months following surgery the small bowel x ray pattern was abnormal and tests of carbohydrate fat and protein absorption showed varying degrees of abnormality (fecal fat 14 24% of intake) Vitamin B_1 absorption however was normal One year after the mesenteric vascular occlusion fat absorption had returned to near normal

► [Syndromes of sublethal intestinal anoxia excape the cynic and ensnare the unwary There is *little* reason to doubt that a massive vascular insult may as reported above impair intestinal absorption and the x ray appearance of a bowel that has suffered segmental infarction may be striking (*1957 58* YEAR BOOK *p 538 J Mt Sinai Hosp New York 26 194 1959*) But what about dyspragia intermittens angiosclerotica intestinalis or intermittent intestinal claudication or more euphonious abdominal angina? At present it may be regarded as a clinical entity that indubitably exists but its recognition is difficult and its threat is that either *more treatable conditions will be passed off as midgut ischemia or* that major abdominal surgery will be undertaken unnecessarily A recent case report appears in the *New England Journal of Medicine* (260 912 Apr 30 1959) —Ed]

Chronic Midgut Ischemia G E Mavor and Wm Michie[4] (Aberdeen Royal Infirm) report 2 cases Midgut ischemia can produce chronic symptoms variously referred to as *intermittent mesenteric claudication abdominal angina and mesenteric stroke* If symptoms are subacute or recurrent repeated incomplete peripheral mesenteric occlusions may be occurring as the result of thrombosis or embolism However constant day to day symptoms as observed in the 2 cases described can be attributed only to persistent ischemia Apparently the period of chronic ischemia *may be punctuated by acute episodes* The symptoms include abdominal pain altered bowel habits weight loss occult blood in the stools and malabsorption the latter leading to diarrhea

CASE 1 —Man 49 had had sudden onset of severe lower abdominal pain associated with vomiting and dark *fluid stools The pain was*

(4) Brit M J 2 534 537 Aug 30 1958

continuous and aggravated by a heavy meal particularly of meats or fats His appetite was poor and he lost 21 lb in 4 months Yellowish feces suggested fat malabsorption Seven months after onset severe abdominal pain occurred lasting for 6 days At laparotomy the small bowel cecum and ascending colon were gangrenous Surgical procedure was not undertaken Autopsy revealed extensive infarction of the bowel due to thrombosis occluding the orifice of the superior mesenteric artery Just inside the orifice was an older organized layer of thrombus that partly occluded the vessel wall

CASE 2—Man 46 had abdominal pain for 9 weeks which was of sudden onset severe felt in the epigastrium unrelated to meals and associated with nausea vomiting and diarrhea The stool was fatty and undigested looking The epigastric pain became intermittent and often worsened after meals He lost 49 lb during 9 weeks At laparotomy no abnormality was noted but the superior mesenteric artery was not examined Two days after operation the patient vomited brownish material and collapsed Autopsy revealed total infarction of the small intestine An old pale red firmly attached thrombus was lying on the posterior aspect of the abdominal aorta from the level of the diaphragm to the bifurcation a similar thrombus extended into the left common iliac artery

In narrowing or occlusion of the superior mesenteric artery with symptoms direct surgery should be undertaken when possible Without surgery extensive bowel infarction is the eventual sequel

Exudative Enteropathy Abnormal Permeability of Gastrointestinal Tract Demonstrable with Labeled Polyvinylpyrrolidone When the plasma protein substitute I^{131} labeled polyvinylpyrrolidone is given intravenously and subsequently gains access to the gastrointestinal tract it is excreted in the feces and the amount present may be determined Robert S Gordon Jr [5] (USPHS) describe a test procedure using labeled polyvinylpyrrolidone and explains the application of this test to patients with so called idiopathic hypercatabolic hypoproteinemia i e severe hypoproteinemia ascribed to a metabolic defect and not related to gross gastrointestinal disease

PROCEDURE—In each subject I^{131} labeled polyvinylpyrrolidone in doses containing 10 25 μc radioactivity is injected intravenously Sufficient potassium iodide is given to prevent thyroidal uptake of any I^{131} that might be liberated Feces are collected for 96 hours in gallon size paint cans The specimens are adjusted to standard gross weight with water treated with 20 Gm phenol to arrest bacterial fermentation and homogenized The specimens together with similarly prepared aliquots of the solution of I^{131} labeled polyvinylpyrrolidone are assayed in a large well type multiple element Geiger counter

(5) La et 1 3 5 326 F b 14 1959

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(5) Lancet 1 325 6 Feb 14 1959

and the fecal I^{131} labeled polyvinylpyrrolidone excretion is expressed as percentage of the do e administered

Fractions of intravenously administered polyvinylpyrro lidone ranging from 0 to 1 5% were found in the feces of normal subjects 4 with nephrotic syndrome 6 with hypo proteinemia due to hepatic disease 3 with hypoproteinemia associated with advanced malignancy and 1 with agamma globulinemia Each of 9 patients with hypercatabolic hypo proteinemia excreted abnormally large amounts of labeled polyvinylpyrrolidone in the feces As would be expected pa tients with the lowest serum albumin levels had the highest percentage of labeled polyvinylpyrrolidone in the feces

The findings implicate the gastrointestinal tract as the route of loss of proteins from the plasma in hypercatabolic hypoproteinemia Because loss of protein into the stomach or intestine is so similar in its metabolic implications to loss via urine or skin it seems appropriate to designate this dis order as exudative enteropathy and to reserve the term hypercatabolic hypoproteinemia to describe true exagger ation of endogenous catabolism Exudative enteropathy like proteinuria is a manifestation of a disease and not a disease entity

► [This harks back to a previous report of hypoproteinemia caused by weeping giant folds of gastric mucosa (1958 59 YEAR BOOK p 536) That the intestinal mucosa may also shed tears of albumin is here elegantly demonstrated by the polyvinylpyrrolidone technic and a companion article is in complete agreement (Lancet 1 327 Feb 14 1959) The question which naturally arises is to what extent fecal los es in malabsorp io syn dromes are literally caused by defective absorption or by excessive exu dation.—Ed]

Intractable Fatal Diarrhea in Diabetic Adolescent Study of Myenteric Plexus R François and Cl Mouriquand[6] (Lyons) report an unusual case

Boy 17 whose stature and weight were those of a boy 11 had had in ulin treatment for diabetes for 5 years Two years before admis sion he had had mumps with no apparent complications About 9 months later a fatty diarrhea appeared with 5 8 stools daily pre dominantly at night At admission he was having 10 30 movements daily either clumped and fatty or decidedly liquid There was partial incontinence and the fecal quantity varied from ½ to 2 L /day There was no blood or mucous membrane Diarrhea was often accompanied by extremely severe abdominal colic The liver was enlarged Neuro logic examination showed absence of knee jerks and diminution in Achilles and anal reflexes The pupils reacted feebly to light and in accommodation

The patient had been receiving 30 units each of insulin and prota

(6) Ann péd at 34 287 87 May 24 1958

mine zinc insulin in a single daily injection Blood sugar was 380 mg /100 ml and 24 hour urine output was 44 Gm Acetonuria pre ent on admission disappeared within a few hours Steatorrhea was incon stant an I stool cultures were negative Blood carotene was decreased to 25 µg /100 ml (normal value 75 100) Barium studies showed gas tric stasis 6 hours after ingestion the stomach was still filled with barium and fluid Functional insufficiency of the small intestine par ticularly segmentation in the ileum was similar to that seen in celiac syndromes

A special diet vitamin B complex pancreatic extract hydrochloric acid and cortisone were all ineffective in controlling the diarrhea Con vulsions and hypoglycemic crises marked the steadily downward course and death occurred 1 month after admission

Macroscopically no pathology was evident. The liver was en larged (1 200 Gm) but appeared normal on section The pancreas presented no gross change or calcification Micro copically the liver showed moderate steatosis with beginning hyalinization in some branches of the hepatic artery Auerbach s plexus in the colon showed numerous changes decrease of ganglion cells hypertrophy and hy perplasia of satellite cell and abundant proliferation of neuroglial fibrillar elements The ganglion cells pre ented varying degrees of degeneration In the jejunum a large fibrotic plexus was observed Meissner s plexus showed minimal changes consisting of slight pro lifer ation of neuroglial cells and alterations in ganglion cells The duodenal mucosa was inflamed but there was no erosion nor atrophy Auerbach s plexus contained numerous ganglion cells which in some places were intact but in many others presented degenerative changes less marked than in the colon the altered plexus usually showed hy pertrophy and hyperplasia of neuroglial elements

Two factors indicate that these findings represent patho logic changes that occurred during life neuroglial hyper plasia is not attributable to an artifact and further altered cells were observed beside others that were morphologi cally normal In the same section Auerbach s plexus was changed whereas Meissner s plexus was normal and in the duodenum some portions of Auerbach s plexus were changed and others were normal There were no vascular lesions nor inflammatory changes and the nerve fibers were not altered

The authors conclude that lesions of the plexus and neuro genic diarrhea of diabetics are certainly related although the mechanism has not been elucidated

► [Gastric atony with prolonged ret ntion of gastric contents and d ar rhea (th m on n nce and nocturnal exacerbation are becoming increas ingly recognized as erious compl cations of severe diabete in the younger age groups It has been assumed that the phenomena are the result of autonomic neuritis postulated to exist a a counterpart of the peripheral neuritis of severe d abetes Ev dence of such an autonomic neuritis has however been lacking in that it has not been demonstrated pathologically

and patients with vagotomy combined with extensive lumbodorsal sympathectomy do not have the gastrointestinal disturbances that the severe chronic diabetic may suffer

This report introduces the possibility that the *responsible* lesion is an Auerbachitis but criteria as to the normal morphology of Auerbach's plexus and normal distribution and number of its cells vary so widely from one pathologist to another that the findings in this case must be regarded as interesting rather than conclusive—Ed]

Massive Gastrointestinal Hemorrhage in Jejunal Diverticulosis was studied by Fred R Denkewalter William Molnar and Alexander P Horava[7] (Ohio State Univ) Jejunal diverticulosis an uncommon condition may give rise to various surgical complications and disease syndromes of which massive upper gastrointestinal bleeding is a rare example Of about 25 reported patients with jejunal diverticulosis with *massive gastrointestinal hemorrhage in only 2 were* definite ulcerations or bleeding points shown on gross or microscopic examination

The authors observed massive gastrointestinal hemorrhage from an ulcerated jejunal diverticulum in 1 patient

Man 68 was hospitalized after passing four dark red black stools during the preceding 48 hours with syncope associated with the last two bowel movements In the previous 8 hours he vomited twice but



Fig 79—Mu l su f f bl di g d ert c l m w th firmly tt hed blood cl t Ulc r h pu h d-o t pp an nd u d bl ed ng po nt (C te y f D nk walter F K et l A S g 148 862 866 N mber 1958)

bright red blood or coffee ground material was not evident After a Levin tube was passed constant low suction yielded clear colorless *gastric* juice which had free acid but only traces of occult blood

Emergency gastrointestinal x ray studies done after stabilization during *the* 2d day showed a normal esophagus stomach and duodenum without *demonstrable bleeding source* There were multiple diverticula the largest the size of a silver dollar arising from the proximal jejunum *Although* no definite ulcer crater was shown within

(7) Ann Su g 148 862 866 N mbe 1958

the diverticula the examiner felt that this possibility should be assumed by exclusion On the 4th day the patient became pale apprehensive and sweaty The pulse rose to 100 with drop in blood pressure to 90/70 This was followed by dark red black stools

At operation multiple loops of blood filled small bowel were noted The stomach and duodenum were normal and contained no blood Several inches distal to the ligament of Treitz multiple blood filled jejunal diverticula were found The largest diverticulum was proximal with each succeeding distal diverticulum decreasing in size On further abdominal exploration no other pathologic lesions were found The segment of the jejunum with diverticula was removed and end-to-end anastomosis accomplished A bleeding ulceration in one diverticula (Fig 79) was seen No other ulcerations or bleeding points were found To date the patient has had no further difficulty

► [At last a report attributing massive hemorrhage to a jejunal diverticulum with documentary evidence to support it! How sensibly different from the many reports that have appeared and alas continue to appear (A M A Arch Surg 77 185 1958) in which massive hemorrhage is unequivocally ascribed to small bowel diverticula and picture of the resected specimen blandly presented without evidence of hemorrhage ulceration or inflammation!

Another convincing report is that of a jejunal perforation discovered with a fishbone protruding from its apex (Ohio M J 54 619 1958) —Ed]

Adenocarcinoma of Jejunum in Nonspecific Granulomatous Enteritis Two authenticated cases of adenocarcinoma of the jejunum arising in long standing granulomatous enteritis have been reported previously but Berthold Weingarten Julia G Parker Eric M Chazen and Harold G Jacobson[8] (Montefiore Hosp New York) present the first report on carcinoma in a bypassed segment of chronically inflamed bowel

Woman 44 had alternating periods of diarrhea constipation and abdominal distention for the first time at age 16 At age 26 roentgen examination showed areas of constriction and dilatation at the junction of the jejunum and ileum and an indurated loop of jejunum Jejunojejunostomy was performed with a blind loop of jejunum remaining About 4 years later symptoms recurred with diarrhea and a 35 lb weight loss Improvement followed conservative treatment but periodic roentgen studies showed increasing stricture and dilatation of the jejunum with delayed emptying At age 44 severe symptoms recurred with a weight loss of 19 lb Another jejunojejunostomy was performed and at operation there appeared to be a closed loop because of a series of constricting adhesions The mesentery was thickened with the sensation of a mass posteriorly Because of the patient s poor condition this was not investigated more closely Some omentum was removed and was found to contain metastatic adenocarcinoma The patient died 2 months after surgery

Autopsy showed regional enteritis involving the jejunum and

(8) A.M.A Arch S g 78 483-489 M h 1959

ileum adenocarcinoma arising in bypassed jejunal loops and metastases to regional nodes peritoneum liver lungs uterus and ovaries

With modern medical therapy including steroids antibiotics transfusions etc increasing numbers of patients with chronic granulomatous enteritis with increasing longevity are to be expected The possible development of adenocarcinoma in a segment of enteritis must be considered in evaluating therapy in these patients

► [In addition to the 3 cases here mentioned 2 more cases of carcinoma complicating regional enteritis have been reported recently (Am J Surg 97 336 1959 Schweiz med Wchnschr 89 266 1959) In view of the small bowel s resistance to malignant degeneration under ordinary conditions these reports assume increasing importance—Ed]

d Pantothenyl Alcohol in Management of Paralytic Ileus Joe W Frazer Benjamin H Flowe and William G Anlyan[9] (Duke Univ) tested the effectiveness of d pantothenyl alcohol (alcohol of pantothenic acid) in treatment of paralytic ileus by comparing two groups of 50 patients each after abdominal operations Each group received customary postoperative care but in addition one group received intramuscular injections of 250 mg d pantothenyl alcohol every 6 hours until normal peristalsis was established whereas the other received a placebo in the same manner

Audible peristalsis occurred in an average of 25 hours in those receiving d pantothenyl alcohol compared to 55 hours in the controls Passage of flatus was noted in an average of 48 hours in the treatment group and in an average of 66 hours in the placebo group Of the 50 patients receiving d pantothenyl alcohol after normal peristalsis returned each continued to complete recovery with no later intestinal dysfunction Of the 50 receiving the placebo in 6 abdominal distention and absent bowel sounds recurred after the usual postoperative period of atony had cleared In 3 of these gastric suction was reinstituted along with multiple enemas and the ileus cleared within 48 hours d Pantothenyl alcohol 250 mg every 6 hours was given to the other 3 2 of whom passed large amounts of flatus within 12 hours and 1 was free from distention within 36 hours

Twelve additional patients selected because they had moderately severe paralytic ileus were treated with d pantothenyl alcohol Within 12 hours peristaltic activity was resumed in all as indicated by audible peristaltic sounds passage of flatus and subjective relief

(9) J A M A 169 1047 1051 Mar 7 1959

Although d pantothenyl alcohol given in the immediate postoperative period appears to facilitate resumption of normal peristalsis after abdominal operations it is debatable whether the actual difference in the average patient is of practical importance The drug is not necessarily needed routinely in unselected patients but prophylactic use might be indicated in those in whom the type and magnitude of intestinal surgery is conducive to development of paralytic ileus

Side effects did not occur after use of d pantothenyl alcohol in this study There was no complaint of excessive abdominal cramps tachycardia and flushing as is so often noted with parasympathomimetic drugs

The most likely theory concerning the mode of action of d pantothenyl alcohol is that it stimulates formation of acetylcholine through the coenzyme responsible for acetylation (coenzyme A) of which pantothenic acid is a component

Treatment of Tapeworm Infestation Report on Effective Treatment without Toxic Effects on Host According to Sidney W Rosen and Everett D Kiefer[1] (Lahey Clinic) the rationale in treatment of tapeworm infestation is to give agents that cause the head of the worm to relax its hold on the mucosa long enough to permit expulsion of the entire worm by strong catharsis If the head or scolex does not come away the worm will regenerate Extract of male fern (Aspidium oleoresin) has never been fully satisfactory

The authors reviewed the records of 40 hospitalized patients in whom infestation was proved by demonstration of proglottides ova or both A therapeutic procedure not requiring toxic drugs was carried out in all Before the treatment is begun these articles should be at the bedside Rehfuss tube 50 cc syringe bottle of glycerin bottle of saturated magnesium sulfate solution thermometer and 500 cc sterile saline solution

TECHNIC—Pass Rehfuss tube into stomach Turn patient on right side and allow tube to pass into duodenum Check tube by fluoroscope to be certain that the tip is well down in 2d or 3d portion of duodenum beyond ampulla of Vater Introduce 1½ oz magnesium sulfate solution through tube Introduce immediately 1½ oz glycerin Introduce immediately 2 oz of a mixture of equal parts magnesium sulfate and glycerin Then introduce immediately 500 cc sterile saline solution which has been warmed to 130 140 F A bedpan should be ready in the patient s room containing warm saline solution so that if the

(1) J A M A 167 065 067 Aug 23 1958

worm is obtained it can be preserved and identified No toxic drugs are required in this procedure

In most instances the entire worm with scolex attached was expelled within 10 15 minutes after treatment Of 40 patients the scolex was identified immediately in 31 In 5 the scolex was not demonstrable Follow up failed to reveal evidence of continued infection Of the other 4 patients 2 did not respond to any degree and did not pass any segments The last 2 were unable to tolerate intubation

► [Since reading this report Dr W D Ashworth in our department, has used the method on 4 patients each attended by entire bodied success but also in 2 instances by syncopal manifestations what with the violent purging —Ed]

Gastrointestinal Intolerance to Oral Iron Preparations is a common complaint according to David N S Kerr and Stanley Davidson[2] (Univ of Edinburgh) Ferrous sulfate ferrous gluconate ferrous succinate ferrous calcium citrate and known and unknown control pills (containing lactose) were administered to 93 healthy young women in a double blind trial Each substance was taken for 5 of 7 days during the total test period of 6 weeks The daily iron intake of 105 mg was the same with each compound The incidence of gastrointestinal symptoms attributed to the pills was assessed from replies to a questionnaire Nausea vomiting heartburn abdominal discomfort constipation and diarrhea were mentioned specifically on the form

Virtually no toxic effects were reported from known control pills containing lactose but the exactly similar unknown control pills which were thought by the subjects to contain iron produced as many side effects as the pills which did in fact *contain it The incidence of all side effects* was 20 25% the commonest symptoms being constipation and abdominal discomfort

A large proportion of the symptoms experienced *during* oral iron therapy thus appears psychologic in origin However the possibility that a few patients have true iron intolerance cannot be excluded

Recurrent Abdominal Pains Field Survey of 1 000 School Children John Apley and Nora Naish[3] included in their series every child in Bristol England who had had at least 3 bouts of pain severe enough to affect his activities over a pe

(2) Lancet 2 489-492 Sept 6 1958
(3) Arch Dis Childhood 33 165 170 Apr 1958

riod of not less than 3 months with attacks continuing in the year preceding the examination The home life the family and the child s personal history behavior intelligence and attainments at school were considered The children were examined clinically and by EEG When 1 000 children with their mothers had been questioned the investigation was stopped Comparable children without abdominal pains were studied as controls

Of the group surveyed 10 8% had recurrent abdominal pains fulfilling the authors criteria Girls were affected oftener than boys In boys aged 5 10 there was a steady in cidence of 10 12% followed after a fall by a late peak at age 14 In girls the incidence was similar up to age 8 This how ever was followed by a marked rise with more than a fourth of all girls aged 9 affected Subsequently there was a steady decrease

In some two thirds of the children with pain it was felt at or around the umbilicus With few exceptions it occurred in the midepigastrium among the rest In about a fourth the pain was severe Attacks of pain were often accompanied by pallor subsequent sleepiness or lethargy headache vomit ing or fever

Recurrent abdominal pains migraine nervous break down peptic ulcer appendectomy and fits were much more common among the families of children with pains than among those without

In the histories of the children themselves appendectomy frequent headaches bilious attacks constipation and asthma were commoner in those with pains than among those with out Tonsillectomy and fits however were commoner among children without pains The incidence of epileptiform ab normalities in the EEG s of the two groups did not support the notion that the recurrent abdominal pains which are so common in childhood are an expression of epilepsy without fits

Though the intelligence of both groups was almost iden tical emotional disturbances were significantly more fre quent in children with abdominal pains Many more of the children with pains tended to be high strung fussy excita ble anxious timid and apprehensive Children with pains tended to drink less milk than the controls Often when dif ficult situations are imminent as at the beginning of school

terms or at examinations the occurrence of pains can be pre dicted Compared with other children those with pains tend to take the ordinary difficulties of life (especially of school life) too much to heart

► [This report shows that milk sensitivity and the even more fanciful diagnosis of abdominal epilepsy are rare causes of abdominal pains in children *Much more important is the emotional state of the child* and above all that of its family —Ed]

Psychogenic Megacolon in Children Implications of Bowel Negativism are discussed by Philip Pinkerton[4] (Univ of Liverpool) In idiopathic or functional megacolon as opposed to congenital neurogenic or aganglionic mega colon no spastic aganglionic segment or other organic le sion can be demonstrated Functional megacolon of this type develops in children due to emotional factors

Nineteen boys and 11 girls aged 2 15 were studied They had histories of functional bowel disorder of 8 months to 15 years duration presenting mainly as chronic constipa tion cumulative fecal retention and overflow soiling Stand ard treatment measures failed and an emotional basis was suspected Fourteen boys and 7 girls who were constipated but had responded satisfactorily to routine treatment proce dures without subsequent relapse were also studied as controls

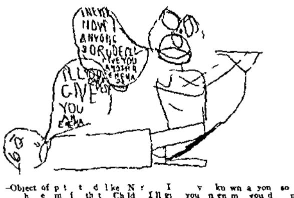
The following factors were etiologically significant pa rental personality characterized by excessive rigidity and/or excessive anxiety primary coercive toilet training parental fears and prejudices relating to constipation and parental overvaluation of the child The primary mechanism involved is a state of negativism on the part of the child ex pressed as persistent refusal to defecate If handled un wisely this state may result in cumulative retention of feces with progressive loading of the rectum and terminal colon and subsequent overflow fecal soiling Ultimately chronic dilatation of the distal bowel develops and is demonstrable by x ray This negativistic pattern develops during the first 3 years of life

Treatment was first directed toward convincing the par ents that what they had formerly regarded as a physical dis order was *in fact* of emotional origin Parental reactions to this approach ranged from frank incredulity through hos tile resistance by obsessional parents or increased concern by

(4) Arch Dis Childhood 33 371 380 Aug t 1958

overanxious parents to simple failure on the part of intellectually limited mothers to appreciate the relationship at all In most instances reassurance was hindered by advice or instruction previously tendered by others about the importance of bowel regularity It was explained that at this stage drastic purgatives would serve no useful purpose and might ► indeed further impair bowel function Therefore it was found advisable to suspend standard treatment procedures apart from insuring adequate fluid intake Parents were advised to practice indifference toward persistence of symptoms

To provide play therapy for patients with psychogenic



Fg 80 —Object of p t t d l ke N r I v kn wn a yon so rid Ill g y h e m f th t Ch ld I ll gi you n en m you d pe t (C rt y f I kerton P A h D Ch ldhood 33 371 380 Augu t 1958)

megacolon the children were encouraged to draw in a sand tray or on paper In addition they were given the opportunity of combining expressive drawing on paper with use of a device known as an aggression board This device permits the child to make a drawing on a large sheet of paper of something he particularly dislikes (Fig 80) to mount this drawing on a board and to lambaste picture and board with bean bags hurled at close range Such treatment encouraging the child to give expression to his hostility led to remission in 21 patients Three proved unamenable to psychiatric therapy

The longest period of absolute constipation through resistance to defecation was 83 days during which the child age 3 was in perfect health

► [Many physicians with a predominantly nonpediatric practice seem

completely unaware that the commonest cause of megacolon with overflow diarrhea and incontinence in younger people is not *Hirschsprung's disease* nor the very rare cases of achalasia of the distal rectal segment (Pediatrics 21 746 1958) but the psychogenic condition here described. Because of purposeful inattention to defecation urges rectal sensitivity to fecal masses is gradually lost a large amount of stool is retained and becomes impacted in the ampulla and material which arrives from above can slither around and leak out In treating these patients local measures such as rectal disimpaction and bowel stimulation are to be used but if the patient s basic negativistic attitude is not changed prognosis is quite discouraging —Ed]

Treatment of Ulcerative Colitis with Local Hydrocortisone Hemisuccinate Sodium Report on Controlled Therapeutic Trial S C Truelove[5] (Oxford Univ) compared the effect of hydrocortisone hemisuccinate sodium used topically with an inert preparation and the combined effect of hydrocortisone and antibiotics as against hydrocortisone alone Patients who went into remission with local treatment were observed to determine the relapse rate on maintenance treatment twice a week

Patients with active ulcerative colitis many of them ambulant received for 7 nights a rectal drip containing either 100 mg hydrocortisone hemisuccinate or 20 30 mg inert preparation (dextran) Each drip was given to 20 patients and observers were unaware of the type of solution used At the end of the first week all patients were given nightly rectal drips of hydrocortisone and antibiotics Penicillin 1 megaunit and streptomycin 1 Gm were added to the hydrocortisone solution In 10 instances neomycin 250 mg was used in place of penicillin and streptomycin

After 1 week 11 patients receiving hydrocortisone and 1 receiving the inert preparation became symptom free There was almost perfect agreement between good clinical response and clear cut sigmoidoscopic improvement Correspondingly the histologic picture of rectal biopsies in the inert group was unchanged whereas in the hydrocortisone group there was a quite definite swing toward histologic mildness

The effect of antibiotics was equivocal In a few patients sharp exacerbation of symptoms was noted especially with neomycin Five patients who did not respond to hydrocortisone alone improved rapidly when antibiotics were added A mixture of penicillin and streptomycin should be added to a rectal drip of hydrocortisone only if hydrocortisone alone

(5) Brit M J 1072 1077 N 1 1958

fails after a week Antibiotics should be stopped if they cause symptomatic exacerbation

Week end maintenance therapy with local hydrocortisone carried out for 6 months did not protect against relapse Some patients were maintained on nightly rectal drips of hydrocortisone for several months without cortisonism In others with ulcerative colitis limited to the rectum and rectosigmoid region 10 mg hydrocortisone once or twice a day in suppositories proved equally beneficial

The advantage of local hydrocortisone over corticoids used systemically is the rapid response and the ab ence of systemic side effects and complications

► (In a companion paper (*Brit M J ? 1077 Nov 1 1958*) Watkinson reports on the use of 100 mg hydrocortisone hemisuccinate dissolved in 100 ml normal saline and given by intrarectal drip for 15 30 minutes on 15 successive evenings Nine of 10 patients so treated had clinical remission but only 1 of 9 receiving a dummy preparation improved As an extension of such studies suppositories containing 10 or 15 mg hydrocortisone acetate or hydrocortisone hemisuccinate have been administered 4 times daily to those with predominantly rectal disease (Gastroenterology 36 490 1959) In ulcerative colitis confined principally to the distal large bowel methods and preparation of this type are well worth trying but their success at least in my hands is quite limited —Ed]

Clinical Significance of Diverticulosis was studied by Russell S Boles Jr and Sara M Jordan[6] (Lahey Clinic) in 294 patients with an average follow up of 15 years Diagnosis of diverticulitis was based on localized pain and tenderness fever leukocytosis and usually a change in bowel habits Average age of patients when first seen was 55 years The sex ratio was about equal A history of definite laxative abuse was present in 40% whereas 11% complained chiefly of diarrhea

When diagnosis was first made the extent of colon involvement was as follows entire colon 33% sigmoid only 22% descending colon 33% transverse colon 10% and ascending colon 2% More extensive involvement was found progressively during the follow up years in 70% of the patients

Complications noted during the ob ervation period in 40% in decreasing order of frequency were diverticulitis hemorrhage obstruction and perforation or fistula In 9 of 16 patients bleeding was in the form of melena Seven patients had diverticulitis and 9 had diverticulosis without evidence of diverticulitis Of 73 patients with diverticulitis

(6) G t ent l gy 35 579 582 Dec mb 1958

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(5) B M J 2 1072 1077 N 1 1958

diarrhea abdominal cramping localized tenderness (often with muscle guarding) fever and leukocytosis were present Of the 503 patients 85 were observed in one or more classic attacks of diverticulitis Of 300 patients who had been ob served 1 5 years only 29 were seen during an episode of in fection Of 49 patients followed 11 18 years 18 (36 7%) were seen in one or more attacks of diverticulitis Only 14% of patients with sigmoid involvement alone had diverticulitis compared with 50% of those with diverticula in all segments of the colon

Medical treatment of diverticulitis was successful and con sisted of rest liquid diet heat to abdomen antispasmodics and Sulfasuxidine® 1 5 Gm 4 times daily Among 85 pa tients gross hemorrhage occurred 7 times rectovaginal fis tula once perforation with peritonitis twice and pericolic abscess 7 times Of 503 diverticulosis coli patients only 2 (0 4%) were operated on

► [Considering that diverticulosis and diverticulitis are so prevalent it is astounding that their natural history remains relatively undescribed. P W Brown and D M Marcley (J A M A 109 1328 Oct 23 1937) reported a follow up of 10 years or more on 76 patients with colonic di verticulosis in not 1 d d symptoms of diverticulitis develop This seems a remarkably low figure particularly in view of all we hear about the complication real or alleged of diverticulosis of the sigmoid. We also are told that surgical treatment for this cond tion is improving that one stage operations frequently can be performed without undue risk for the patient and that we should operate earlier and oftener on patients with diverticulit s of the sigmoid If we are to decide on this question intelli gently we *must* know more about the natural history of diverticulos s and *diverticulitis so that we can accurately compare in pondering surgery* the advantages and risks of doing nothing (medical treatment to my mind i more or less doing nothing) and those of undertaking surgery

The 2 papers here abstracted report considerable advances in rectifying the situat on Both it is to be noted indicate that the prognosis even of diverticulitis and some of its complications is relatively benign The situa tion is thus somewhat like that pertaining to gallstones Of the many many people with diverticulosis and diverticulitis of the colon only a small fraction have serious developments such as bowel obstruction fistula, profuse hemorrhage or abscess format on with portal pyemia On the other hand since there are so many with these bowel pouches the absolute num ber com ng to the surgeon with complications is considerable and he impressed by this number argues for earlier surg cal intervention possibly more enthusiastically than he should

Retrospective analyses of a se ies of patients in a single treatment expe rience may be misleading on several counts The patient group selected by the type of practice the nterests of those making the study and incom plete or inaccurate follow up are always possible sources of error Fur ther Horner finds that durat on of follow up grossly influences the results The figures reporting the incidences of diverticulitis in patients followed 11 18 years and in patients with generalized colonic as opposed to sig moidal diverticulos s *probably mean that the more d verticula a patient*

38% had superimposed complications whereas of 221 patients with only diverticulosis 8 1% had complications without evidence or history of clinical diverticulitis Of the 73 with diverticulitis 40 had only 1 attack during the period of observation 16 had 2 attacks 7 had 3 attacks and the rest had 4 6 attacks Almost half the group had no further attacks during a follow up of 11 27 years With multiple attacks of diverticulitis there was an increase in superimposed complications—obstruction bleeding or perforation and fistulas—affecting over one half of 33 patients with more than 2 attacks

Whereas no patient with uncomplicated diverticulitis required surgical treatment 16 of 28 patients with complications underwent surgery Among 294 patients with diverticulosis cancer developed in 5 4% In 221 patients without diverticulitis the cancer rate was 4% whereas in those with diverticulitis it was 9 6% (7 patients) However in 4 of these cancer developed in an area where there were no diverticula

It is felt that diverticulitis is a medical disease until complications make surgical treatment necessary

Natural History of Diverticulosis of Colon was studied by John L Horner[7] (Washington Univ) in 503 patients (53% women) with x ray evidence of colonic diverticula In about 95% some or all of the colonic diverticula were in the sigmoid Present or past obesity was unimportant etiologically Constipation occurred in 14% Symptoms when present were indistinguishable from the irritable colon syndrome Progression in number size or distribution of the diverticula or all three could clearly be seen in 54 patients during an average interval of 5 1 years between repeat examinations In 129 patients with an average interval of 4 4 years between examinations no progression could be seen Some of these were examined over a period of 10 or more years

In patients who avoided foods which leave rough undigested particles in the stool and who when constipated kept the stool softened with small nightly doses of mineral oil mucilages or wetting agents difficulties rarely developed thus demonstrating the benign natural history of diverticulosis coli

Diverticulitis was diagnosed when acute constipation or

(7) Am J Dig t. Dis 3 343 350 May 1958

found in a polyp free or a polyp containing large bowel Between ages 31 and 50 cancers were found in polyp containing bowel more often than could be accounted for on the basis of chance but there are other explanations besides the one polyps become cancer

The malignant potentialities of cancerous cells in a polyp depend on whether or not the stalk is invaded If not invaded the lesion does not behave biologically as cancer Invasion of a stalk by a cancer originating in a previously existing benign polyp can be defined as truly malignant but if this sequence occurs various stages in the extension of the lesion from the body of the polyp through the stalk and into the bowel wall should be discoverable In examining 323 colonic cancers however no recognizable polyp tissue was found and among 425 adenomatous polyps only one questionable instance of infiltration of the stalk by a cancer arising in a polyp was discovered

The authors conclude that no real evidence can be found that adenomatous colonic polyps become infiltrating metastasizing cancers

► [One gets the impression that the authors attitude although critical is not one of entire disbelief They do not say that polyps cannot be cancer seeds they merely point out that present evidence does not warrant such statements as It is generally agreed that adenomatous polyps eventually develop into clinical cancer —Ed]

Studies on Ameba Bacteria Relationship in Amebiasis II Some Concepts on Etiology of the Disease are discussed by Bruce P Phillips Patricia A Wolfe and Ida Louise Bartgis[9] Endameba histolytica introduced intracecally into conventional guinea pigs produces ulcerative amebiasis When the ameba is introduced into germ free guinea pigs however it neither produces disease nor survives Hence it appears that the etiologic role of E histolytica may depend on one or more of its microbial associates in the intestine

Certain environmental characteristics of the germ free intestine were studied The oxidation reduction potential and pH values of the cecal lumens of germ free guinea pigs were ascertained These were compared with values obtained in conventional guinea pigs and evaluated with respect to their adequacy for permitting amebic growth Though the oxidation reduction potential was higher in the germ free group no significant differences were noted in pH values

[9] — J Trop Med 7 392 399 July 1958

has and the longer he has them the greater is the chance that one or more of them will become infected

Perhaps the more serious criticism that must be leveled at retrospective analyses of this type is the lack of control series Obviously such control groups are very difficult to establish and maintain in clinical practice and the mere absence of controls should not keep a man from publishing the results he has obtained In many aspects they may be most valuable However authors of such retrospective analyses must be meticulous in banishing their preconceived ideas which otherwise tend to creep in and distort the real value of their observations Thus Horner's concepts as to the value of a bland diet and a soft stool are merely what he believes to be the explanation for the relatively benign course of his patients He has no data on the fate of patients who ate unrestrictedly and were healthfully unconcerned about the consistency of their feces—Ed]

Relationship of Polyps of Colon to Colonic Cancer is evaluated by John S Spratt Jr Lauren V Ackerman and Carl A Moyer[8] (Washington Univ) by analyzing distribution incidence and morphologic characteristics of colonic polyps and cancers in several tumor populations If polyps act as cancer seeds (1) the distribution of polyps and cancers in the colon should be congruent (2) the distribution of polyps about coexistent cancers should be random (i e the chances for a polyp to lie above or below a coexistent cancer should be equal) and (3) the distribution of cancers associated with polyps should be determined by the distribution of the polyps and should differ from the distribution of colonic cancers not associated with polyps Statistical analysis of the distribution of 243 single colonic cancers 53 with associated adenomatous polyps and 190 without associated polyps revealed that the relative distributions of the cancers and polyps did not show the congruence and randomness to be expected if benign polyps are the precursors of cancers and the coexistence of polyps did not significantly alter the distribution of cancers as compared to the distribution of cancers found without polyps Further in 16 cases of familial polyposis the distribution of 12 cancers was the same as that to be expected in colons containing no polyps though the patients had hundreds of fairly evenly distributed adenomatous polyps

If adenomatous polyps are loci for the growth of adenocarcinomas in the colon the frequency of cancer should be distinctly higher in polyp bearing than in polyp free colons In over 1 000 colons examined at autopsy by Helwig the frequencies with which cancers occurred in the colon with and without polyps in the age groups 50 80 were what they should be if chance alone determined whether cancer is

(8) A S g 148 68 698 O t be 1958

diarrhea suggested that the cause was bacteriologic or toxic rather than parasitic Theories that the excitement of travel change in daily routine or variation in climate are responsible for the diarrhea of tourists are contraindicated by the low incidence of diarrhea among visitors to Hawaii

► [This may sound like an advertisement to go to our 50th state rather than to Mexico but the trip to Mexico is still worth it despite the fact that 1 out of 3 of you will have diarrhea Furthermore as medical conventioners at some of our Atlantic Coast resorts can attest turista is not confined to him who ventures south of the Rio Grande —Ed]

LIVER GALLBLADDER AND PANCREAS

The story of bilirubin metabolism which has been unfolded in articles abstracted in the YEAR BOOK OF MEDICINE in the past 5 years is now fruiting with many studies developing the field and extending its boundaries Since the parent idea is relatively young its offspring are all relatively novel and this accounts for the fact that as many as 8 abstracts devoted to this subject appear on the following pages The questions which have been explored include

1 What are the details of hepatic conjugation of bilirubin and is conjugation with glucuronic acid the only pathway?

2 Can the bile pigment accumulations in the blood that characterize various forms of jaundice be explained in terms of specific biochemical mechanisms in various forms of hepatobiliary disease?

3 Is the diagnosis of various forms of jaundice facilitated by the new found knowledge?

4 Has our new knowledge concerning bilirubin metabolism affected the management of patients with jaundice?

As is evident in the succeeding abstracts the newer knowledge of bilirubin metabolism has found its chief application in elucidating jaundice in the newborn and in particular those syndromes dependent on rapid hemolysis on one hand and deficient conjugating mechanisms on the other From the therapeutic point of view emphasis has been placed on the toxicity of unconjugated relatively water insoluble bilirubin and the consequent advantages of converting this to the conjugated form as rapidly as possible In the hepatobiliary types of jaundice that affect the adult however the diagnostic and therapeutic advantages of knowing more

In 2 of 5 germ free animals which received sodium thioglycolate and 13 of 22 which received l cysteine as reducing agents with amebic inoculum amebic lesions developed However in no instance were multiple lesions of the intestine observed Amebic lesions occurred within traumatized cecal wall areas in 4 of 12 germ free animals after inoculation *Among 50 germ free guinea pigs fed autoclaved cecal con* tent from conventional guinea pigs before and after amebic inoculation amebic lesions developed in 16 In 15 only a local lesion developed Among 8 animals with intracecal amebic inoculation which received Bacillus subtilis as a contaminant amebic lesions developed in 7 Four had multiple lesions with extensive ulceration of the cecum and in the upper colon nearest the cecum

It is felt that bacteria are involved essentially in the etiology of intestinal amebiasis Within the intestine of the host they provide an environmental physical and/or chemical in which the ameba may become established and grow

Diarrhea of Travelers I Incidence in Travelers Returning to United States from Mexico is evaluated by B H Kean and Somerset Waters[1] At the Los Angeles International Airport during 1 month 1 265 United States residents arriving by air from Mexico were asked to fill in a questionnaire as were 210 tourists returning from Hawaii

Of those who spent a week or more in Mexico 33% re*ported that they had one or more attacks of* diarrhea Of these 63% became ill during the 1st week in Mexico 32% within the 2d week 4% during the 3d or 4th week and 1% after 5 weeks The number of men and women affected were about equal Incidence was highest among persons under age 24 The diarrhea lasted for 1 day in 57% 2 3 days in 32% 4 5 days in 7% and for 6 days or more in 4% Completely confined to living quarters by the attack were 13% No treatment was undertaken by 20% whereas 71% took medicine Of those who visited Mexico often and stayed 7 days or longer on this trip only 13 5% had diarrhea compared with the over all incidence of 33%

Only 7 6% of the visitors to Hawaii who stayed a week or *more reported* diarrhea

Immunologic factors may be responsible for the greater susceptibility of the younger age groups Time of onset of

(1) A M A Arch Ind Health 18 148 150 Aug 1958

points *1* and/or *1* the *H* at these points being replaced by the glucuronic acid shown in boldface type in formula I

Sulfate conjugation with bilirubin takes place at points *2* and/or *2* i e at the hydroxyl groups

In the Van den Bergh reaction bilirubin is exposed to diazotized sulfanilic acid (DSA) One molecule of DSA splits the bilirubin molecule at *3* or *3* and then joins the half bilirubin molecule at the same site to form an azopigment A second molecule of DSA then reacts with the remaining half molecule of bilirubin at the analogous remaining site and the methane bridge (—CH —) is liberated

If the half molecule of bilirubin carries a glucuronic acid molecule at *1* the azopigment is designated B if the half bilirubin i unconjugated at *1* azopigment A is formed

A molecule of unconjugated bilirubin (shown above) produces when diazotized two of pigment A bilirubin diglucuronide two of pigment B and bilirubin monoglucuronide one of pigment A and one of B

Studies on Bilirubin Sulfate and Other Nonglucuronide Conjugates of Bilirubin It is known that direct reacting bilirubin is a polar and water soluble conjugate of bilirubin Recent inve tigations provide evidence that this conjugate is a diglucuronide that forms primarily in the liver and that the glucuronic acid is attached at the two carboxyl groups of the bilirubin molecule Because hepatic conjugation of alcoholic and phenolic compounds such as corticosteroids and estrogens involves formation of sulfate as well as glucuronide derivatives Kurt J Isselbacher and Elizabeth A McCarthy (Harvard Med School) thought that an ethereal sulfate derivative of bilirubin at its hydroxyl groups might also occur The authors provide evidence of the physiologic occurrence of bilirubin sulfate as well as other as yet unidentified nonglucuronide conjugates of bilirubin in the bile of animals and man

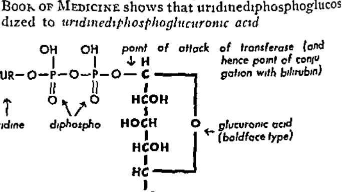
After injection of radioactive sulfate bilirubin sulfate was identified in the bile of rats cats and man Injection of the radioactive sulfate resulted in excretion of many radioactive products in bile as shown by paper chromatography and autoradiography After purification by extraction procedures followed by adsorption and elution from Zn(OH) gel one major radioactive metabolite remained that migrated with

(2) J Cl I t 38 645 651 April 1959

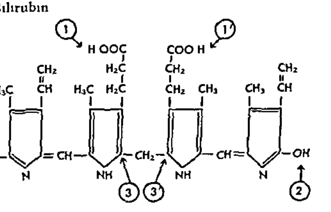
about bilirubin metabolism have been less evident The interacting complexities of cholestasis and liver damage make it difficult to explain jaundice on the basis of one specific biochemical defect and even in Gilbert s syndrome as seen in the average case (i e with a mild bilirubinemia usually not exceeding 4 or 5 milligrams per cent) it is hard to be sure that a specific transferase defect leading to impaired conjugation is responsible Incidentally an excellent review of Gilbert s syndrome may be found in Medicine 38 25 1959

As an aid to understanding the following abstracts some formulas may be helpful

I The scheme reproduced on page 569 of the 1958-59 YEAR BOOK OF MEDICINE shows that uridinediphosphoglucose is oxidized to *uridinediphosphoglucuronic acid*



II Bilirubin



Glucuronide conjugation with bilirubin takes place at

Subsequently the azopigments are extracted separated by simple partition between butanol chloroform and acetate buffer and estimated colorimetrically The proportions of mono and diglucuronide in the direct reacting bilirubin are calculated from the relative quantities of azopigments A and B found The entire procedure was routinely completed within 30 minutes to minimize possible hydrolysis of azo pigment B Values obtained were reproducible and results of estimations of the per cent of mono and diglucuronide in direct reacting bilirubin of bile urine and plasma agreed with the values obtained by others by column chromatography

Bilirubin diglucuronide accounted for ~4% of the direct reacting bilirubin in human T tube bile specimens In 23 patients with nonhemolytic jaundice bilirubin diglucuronide accounted for 81% of the direct reacting bilirubin in the urine but in 17 of these bilirubin monoglucuronide was the major fraction in the plasma Monoglucuronide levels ranged from 55% to 65% in 15 patients including most of those with viral hepatitis and 3 with extrahepatic biliary obstruction for over 2 months Monoglucuronide levels ranged from 67% to 88% in 6 patients including 2 with portal cirrhosis 2 with diffuse intrahepatic carcinoma and 1 with secondary biliary cirrhosis for over 8 years Relatively low values were observed in 1 with acute choledocholithiasis (32% mono glucuronide) 1 with viral hepatitis at onset of jaundice (43%) 1 with cholangiolitic hepatitis (48%) and 1 with hemochromatosis (45%)

Experimental and clinical studies described by Bollman indicate that bilirubin is conjugated to the diglucuronide only in the liver and may accumulate in the blood after acute biliary obstruction Bilirubin monoglucuronide can be synthesized in extrahepatic tissues and may accumulate in the blood in hepatectomized animals and in patients with hepatic parenchymal disease Because almost 60% of the patients studied by Schachter comprised an intermediate group with monoglucuronide levels of 55-65% estimation of the glucuronides in plasma is of limited diagnostic value though high diglucuronide levels suggest acute biliary obstruction and high monoglucuronide values suggest hepatic parenchymal disease

► [The amount of direct reacting bilirubin measured in a sample of

the conjugated azopigment of bile When this band was eluted and rechromatographed in any of three solvent systems the radioactivity still remained with the azopigment band Acid hydrolysis of this eluted labeled pigment resulted in liberation of radioactive inorganic sulfate as noted by chromatography Taurine was not detected as a product of this hydrolysis In rats with surgically ligated bile ducts labeled conjugated azobilirubin pigments were found in bile in urine after injection of radioactive sulfur Chemical studies with hydroxylamine and diazomethane suggest that the sulfate is linked at the hydroxyl groups of bilirubin Additional evidence for occurrence of nonglucuronide conjugates of bilirubin was provided by presence of a conjugated azobilirubin fraction that resisted beta glucuronidase hydrolysis and contained no glucuronic acid

Analyses of the bilirubin azopigments in 11 T tube samples of human bile revealed mean beta glucuronidase resistant fraction of 23 7 ± 6 4% mean bilirubin sulfate content of 13 7 ± 5 6% and alkali stable residue with mean of 15 0 ± 6 2% These data suggest that there is yet another conjugated azobilirubin fraction amounting to 9 10%, which is alkali labile and contains no glucuronic acid or sulfate Considering other known hepatic conjugation mechanisms these conjugates may be methyl or glycine derivatives of bilirubin linked at the carboxyl group

Possible bilirubin conjugates containing glucuronic acid and sulfate occur as in the case of morphine In liver disease variations in the percentage of excreted glucuronide or sulfate derivatives may take place In vitro observations indicate that the total glucuronide conjugating capacity of the mammalian liver declines with experimental liver damage

Estimation of Bilirubin Mono and Diglucuronide in Plasma and Urine of Patients with Nonhemolytic Jaundice David Schachter[3] (Columbia Univ) describes a simple method for estimating mono and diglucuronide in direct reacting bilirubin in which the relatively labile bilirubin glucuronides are initially coupled with diazotized sulfanilic acid (direct van den Bergh reaction) to yield the stable azo pigment derivatives In the reaction 1 mol of diglucuronide yields 2 mols of azopigment B and 1 mol of monoglucuronide yields 1 mol of azopigment A plus 1 mol of azopigment B

(3) J Lab & Cl Med 53 557 56 April 1959

with obstructive jaundice showed increased secretion of glucuronic acid after salicylamide

Of the 4 patients with Gilbert s disease all had been jaundiced in the past but only 1 had increased serum bilirubin level when salicylamide was given All excreted normal amounts of glucuronic acid after the challenge This suggests that the jaundice of Gilbert s disease may not be due to inability to conjugate bilirubin with glucuronic acid or that the defect may be intermittent brought on by minor stresses and strains Conjugation of salicylamide in these patients may not have occurred only in the liver another possible site is the kidney

The 1 patient with Dubin Johnson syndrome showed normal glucuronic acid output before and after salicylamide This is not surprising because the defect in this disease is not in conjugation and most of the bilirubin in the serum is in the direct form

► [Glucuronic acid conjugation is a metabolic function employed by the liver to handle many substances in addition to bilirubin menthol phenols salicylates and metabolites of cortisol Many of these substances including salicylamide may also form glucuronides at sites outside the liver and to this extent tests as here described may not provide a quantitative assessment of hepatic glucuronide conjugating capacity —Ed.]

Studies on Kernicterus Relationship with Sulfonamide Intoxication Report on Kernicterus in Rats with Glucuronyl Transferase Deficiency and Review of Pathogenesis Kernicterus occurs in rats of a strain with familial hyperbilirubinemia (Gunn s strain) These animals lack ability to convert indirect bilirubin into direct reacting bilirubin (conjugated bilirubin) that can be excreted by the liver This conversion is achieved by fixation of two molecules of glucuronic acid on the indirect bilirubin Conjugation occurs in the liver and requires uridine diphosphate glucuronic acid and the enzyme glucuronyl transferase Activity of this enzyme in vitro is extremely low in the liver of adult homozygous Gunn rats and is below normal in heterozygotes though these animals have no hyperbilirubinemia

William A Blanc and Lois Johnson (New York) made clinical and morphologic observations in many Gunn strain rats including homo and heterozygotes They found that the clinicopathologic syndrome of kernicterus in rats with congenital deficiency of liver glucuronyl transferase is sim

(5) J N p th & E p N l 18 165 189 J ry 1959

plasma depends on how long the coupling reaction between bile pigments and diazotized sulfanilic acid is allowed to proceed Malloy and Evelyn s technic (J Biol Chem 119 481 1937) employed a 30 minute interval Ducci and Watson s 1 minute Schachter used 5 minutes and credits the direct reaction as carried out by him as being specific for conjugated bilirubin Perhaps the popular 1 minute method of Ducci and Watson measures smaller amounts of the monoglucuronide Whatever method is used, however and even if mono and diglucuronides of bilirubin are individually fractionated the partition of plasma bile pigments still appears to have quite limited diagnostic value—Ed]

Urinary Glucuronic Acid Excretion in Liver Disease and Effect of Salicylamide Load Bilirubin is liberated from the breakdown of hemoglobin in the reticuloendothelial system and gives the indirect van den Bergh reaction It is transformed to direct reacting bilirubin by conjugation with one or two glucuronic acid molecules to form bilirubin mono or diglucuronide The diglucuronide is almost certainly formed exclusively in the liver the monoglucuronide in other sites also

H T F Barniville and R Misk[4] (Postgrad Med School London) investigated the ability of the liver to perform this conjugation in congenital hyperbilirubinemia and in various liver diseases Of 40 subjects studied 12 were controls who had no evidence of liver disease Of the 28 patients 14 had portal cirrhosis 3 had primary biliary cirrhosis 6 had extra hepatic obstruction of the biliary passages 4 had Gilbert s type of hyperbilirubinemia and 1 had Dubin Johnson type of hyperbilirubinemia Daily urinary excretion of glucuronic acid in these subjects varied widely but was higher in presence of jaundice (mean 692 mg) than in its absence (mean 468 mg) However no relationship could be found between the amount of glucuronic acid excreted and the depth of jaundice The 12 controls showed mean excretion of 395 mg daily

After an oral dose of 4 Gm salicylamide 24 hour urine output of glucuronic acid increased greatly presumably owing to conjugation of salicylamide with glucuronic acid Six normal subjects showed mean excretion of 4 078 mg 4 patients with portal cirrhosis without jaundice also showed pronounced increase Four patients had markedly defective ability to increase urinary glucuronic acid output after salicylamide All had severe hepatocellular jaundice 3 had advanced portal cirrhosis and 1 had decompensated secondary biliary cirrhosis Three with primary biliary cirrhosis and 3

(4) Brit M J 1 337 340 Feb 7 1959

Treatment of Hyperbilirubinemia of Newborn with Sodium Glucuronate is advocated by Stuart Danoff Audrey Boyer and L Emmett Holt Jr [6] (New York Univ Bellevue Med Center) Because indirect unconjugated bilirubin is toxic to the brain and because the newborn infant conjugates bilirubin inefficiently 25 infants with bilirubinemia exceeding 9 5 mg /100 ml were given sodium glucuronate in an effort to promote conjugation and hence excretion of bile pigments Sodium glucuronate was given intravenously or by clysis as a 2 3% solution in 5% glucose the total varying from 2 to 47 Gm and the rate from 100 to 250 mg /kg / hour In 17 infants indirect bilirubin started to fall within 3 hours of glucuronate administration and decreased by more than 5 mg in 24 hours In 5 a rising bilirubin concentration leveled off or began a slow decline In 4 no effect was noted Intravenous glucuronate appeared more effective and less attended by complications than glucuronate given by mouth

Theoretically conjugation of indirect bilirubin requires first formation of uridine diphosphate glucuronic acid then enzymatic transfer of this prepared glucuronic acid to the bilirubin It is possible however that an inefficient transfer system may be speeded up by mass action if larger amounts of plain glucuronic acid are given If such a mechanism explains the results obtained it is not clear where the bilirubin goes when its level falls in the blood serum though in 3 instances increased urinary excretion of bilirubin was found after therapy

Another and more disturbing explanation for the results is that glucuronate alters the distribution of indirect bilirubin and may drive the pigment into the tissues and brain an effect apparently produced when glucuronate is given to genetically jaundiced rats with high serum unconjugated bilirubin levels In infants however there is no evidence of increased tissue pigmentation after glucuronate administration Further trial of this therapy is warranted especially since therapy by means of exchange transfusions is not devoid of risk

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(6) P d t 23 570 577 M h 1959

ilar to the syndrome of human kernicterus The physico chemical properties of intracellular bilirubin appear to be those of unconjugated (indirect) bilirubin The earliest de tectable changes in ganglion cells are associated with the presence of intracellular bilirubin This is compatible with the concept that bilirubin is the toxic agent

Silverman *et al* have reported a correlation between oc currence of kernicterus and prophylactic Gantrisin® ad ministration in premature infants There was no difference in mean levels of the bilirubinemia between the group of infants with kernicterus and those who died without kernicterus Because bilirubin in increased amounts could not be im plicated as the sole factor in production of kernicterus in these infants the present authors studied toxicity of Gan trisin® in newborn albino rats The drug had no toxicity in these rats when injected at doses up to 500 mg/kg/day for 1 month No icterus hemolysis brain liver or pancreatic damage could be detected When Gantrisin® treated and control newborn rats were supravitally perfused with bili rubin trypan blue or methylene blue no evidence of altered blood brain barrier was obtained

Although Gantrisin® did not affect normal rats treatment with sulfonamides has been correlated with a drop in bili rubinemia and appearance of kernicterus in both premature infants and Gunn strain rats This suggests that these drugs induce shift of bilirubin from the vascular bed into other body compartments A similar mechanism may be operative in kernicterus occurring under other circumstances Once present in the extracellular space bilirubin may exert its well demonstrated deleterious effect on the cell alter the cell membrane permeability and combine with cytoplasmic structures Selective staining of certain brain nuclei may be due to selective affinity of some component of their cells for unconjugated bilirubin as well as to individual variation of cell permeability or resistance to bilirubin toxicity Nothing is known about the amount of bilirubin required to induce cellular death the time required to produce lethal effect or reversibility of the changes

► [To the list of eponymically famous animals—Shay rat, Pavlov dog etc.—add the Gunn rat —Ed]

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(6) Ped t 23 570 577 M h 1959

from 15 to 31 mg (average 21 mg) 40-72 hours after birth

During the same period 189 prematures were born to mothers who did not receive Hykinone® Incidence of unexplained hyperbilirubinemia in this group (serum levels over 20 mg/100 ml) was 8% This is within the range reported by other authors

Major blood group incompatibility existed in only 1 of the 7 infants with hyperbilirubinemia born to mothers who had received Hykinone® All the infants had a negative Coombs test The mothers all had negative serologic tests for syphilis None of the infants was suspected of having sepsis before exchange transfusion All received 2 5 mg Hykinone® intramuscularly at birth and 2 5 mg on the 3d day This amount has not been shown to affect serum bilirubin levels One infant died on the 4th day and at autopsy was found to have kernicterus

The authors hypothesize that the vitamin K analogue passed through the placenta and exerted hepatotoxic effect on the 7 infants with hyperbilirubinemia Perhaps vitamin K analogues which are partially conjugated with glucuronide compete with glucuronyl transferase Preliminary experiments suggest that Hykinone® is hepatotoxic when given to Gunn rats

► [A confirming report (Obst & Gynec 13 41 1959) incriminates 5 mg of a water soluble vitamin K preparation given intramuscularly to mothers immediately pre partum Most of the infants also received 2 5-5 0 mg vitamin K at birth —Ed]

Prolonged Obstructive Jaundice in Infancy V Genetic Components in Neonatal Hepatitis are evaluated by David Yi Yung Hsia Joseph D Boggs Shirley G Driscoll (Chicago) and Sydney S Gellis[1] (Boston) A syndrome of prolonged obstructive jaundice in infancy not associated with erythroblastosis fetalis or biliary atresia is characterized by onset of jaundice in the first weeks of life acholic stools dark urine and moderate hepatomegaly and splenomegaly Flocculation tests of liver function are usually negative One minute and total serum bilirubin are always elevated and show a slowly falling or variable trend Histologic examination of the liver reveals focal or widespread hepatocellular degeneration often with formation of multinucleated liver cells Because of its uncertain cause the disease state has been variously termed neonatal hepatitis infantile hepatitis

(1) A.M.A J D Child 95 485-491 May 1958

giant cell hepatitis or merely the inspissated bile syndrome of unknown etiology

The authors analyzed 59 families with 1 or more cases of neonatal hepatitis from the genetic viewpoint There was a total of 120 children in the 59 families After excluding the index case in each family there were 11 affected and 50 normal siblings Thirty three families with infants with atresia of the bile ducts were studied as controls These cases seemed most appropriate for comparison because in them jaundice also develops in early infancy and often the condition cannot be differentiated from neonatal hepatitis on clinical or laboratory grounds After excluding the index cases there were 40 siblings and in none of these did jaundice develop The difference is highly significant

There was little in the data to suggest that neonatal hepatitis is transmitted as a mendelian dominant however analysis by the Weinberg sib method showed the trait to be consistent with an autosomal recessive mode of inheritance In 13 families 1 or more children were born after birth of the infant with neonatal hepatitis There was random distribution of affected and normal infants in these pregnancies following birth of the index case

Forty one infants recovered from neonatal hepatitis and 27 showed sequelae or died outcome in 2 infants was unknown Sex and birth order did not appear to influence prognosis and complications were greater in families with multiple cases

Although this analysis shows good genetic fit for an autosomal recessive mode of inheritance this does not indicate that neonatal hepatitis is actually a hereditary condition However this new dimension must be added to thinking on the subject because theories implicating inclusion cell virus the virus of infectious hepatitis or the virus of homologous serum hepatitis have various imperfections If an intrauterine factor is responsible for neonatal hepatitis the morphologic changes might be the result of some insult to the liver occurring early in embryonic life and in some way genetically determined

► [This abstract has been included not only because of its intrinsic interest but to remind us that syndromes other than those related to red cell hemolysis *may account for the icterus of infancy A consideration that* may complicate the authors argument is that viruses may themselves

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(1) A M A J Dis Child 95 485-491 May 1958

the needle preventing the cylinder of biopsy tissue from being drawn into the syringe (Fig 81 *A C*) It also regulates the force of aspiration which should be continuous and constant but not too violent This blocking device constitutes the chief difference between this needle and types previously used

Biopsy is performed between the anterior and posterior axillary lines in the intercostal space corresponding to the point of maximal hepatic dullness Anesthesia and perforation of the skin are performed next A syringe containing 3 ml sterile saline solution is attached to the needle which is inserted at right angles to the skin to a depth of 4-5 cm About 2 ml saline is injected to wash skin fragments out of the needle The patient is instructed to breathe out fully and then stop breathing With the piston of the syringe pulled out to the 4 or 5 cc mark to produce suction the needle is advanced quickly for its entire length without rotation and then extracted rapidly After extraction the syringe must be kept in the position of aspiration to prevent loss of the liver tissue The tip of the needle is immersed in isotonic saline solution and aspiration is gradually released The plunger is carefully pushed to expel the physiologic saline solution remaining in the syringe thus expelling the biopsy material

Advantages of the technic are its rapidity simplicity inexpensiveness and elimination of complicated maneuvers during the procedure The procedure has been nearly 100% successful Risk is greatly reduced and the biopsy is almost painless Microbiopsy using the 1 mm needle is particularly well adapted to extensive exploration of the morphology of the liver since biopsy may be performed at more than one point with minimal inconvenience or danger to the patient Contraindications are limited to hemorrhagic diseases and hydatid cysts

► [The technic has been well received Needles may be obtained at this address

Societa ICO
Piazza Galileo 6
Bologna Italy—Ed]

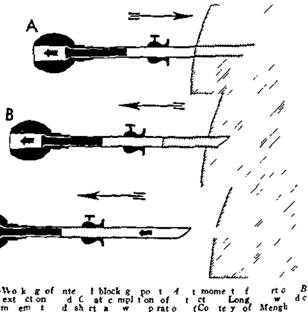
Microbiologic Test for Hepatitis Epidemica A Burgherr[3] (Central Lab Swiss Red Cross Bern) found that serums from patients with infectious hepatitis inhibit spore germination of the fungi Helminthosporium sativum and Alternaria tenuis The fungi are inoculated on an agar plate containing 1 ml fasting serum are incubated and the germinated spores are then counted under the microscope (the number of germinated spores found among 250 spores is called the germ count)

The author tested 62 serums of blood donors with a history of jaundice and 62 of control donors without such a history

(3) Schw Zts h llg P th 22 177 01 1959

affect genetic factors and thus play a role in apparent genetic relationships —Ed.]

One Second Needle Biopsy of Liver The average duration of the intrahepatic phase of needle biopsy of the liver varies from 4 to 15 seconds in the technics commonly used Giorgio Menghini (Univ of Perugia) describes a method which reduces the intrahepatic phase to about 1 second using a



F g 81—Wo k g of nte l block g po t A t mome t f rt o B at beg ng of ext ct on d C at c mpl t on of t ct Long w d c t d rect n of m em t d sh rt a w p rat o (Co te y of Mengh G Gast oent logy 35 190 198 A gu t 1958)

simple inexpensive maneuverable instrument of small diameter

TECHNIC —The needle is made in three diameters 1 4 mm 1.2 mm and 1 mm the 1 2 mm needle being preferred for routine use The cannula is 7 cm long less than half the length of the Iversen needle and its walls are as thin as possible (0 09 0 15 mm) An adjustable guard may be used to limit depth of penetration The tip of the needle is oblique and slightly convex toward the outside permitting a uniform easy continuous cut of the tissue without rotation of the instrument There is no stylet but an internal blocking device is provided This device is a cylinder with a flange at the proximal end The cylinder is 3 cm long with a diameter about 0 2 mm less than the internal diameter of the cannula The diameter of the flange is greater than that of the cannula and greater than that of the internal diameter of the tip of the aspirating syringe The device blocks the tube of

(2) Ga t oente l gy 35 190 198 A gu t 1958

without extensive necrosis The liver cell plates were interrupted throughout the lobule by necrosis of single or groups of liver cells which were replaced by inflammatory cells The variation in size and staining qualities of the liver cells in the same area was the outstanding feature of the process The Kupffer cells were mobilized and contained as did intralobular macrophages much brown lipofuscin pigment apparently derived from liver cell breakdown Many bile canaliculi were dilated and contained bile plugs The borders of the portal tracts were obscured by proliferation of ductules some of which contained bile plugs and exudate cells in their irregularly widened lumens

In a case of subacute hepatitis the centrolobular zone exhibited severe bile stasis hepatocellular degeneration and necrosis whereas in the intermediate zone regeneration with multinucleated giant cells and acidophilic bodies was noted

Study of autopsy specimens revealed two types of change In one characterized by acute necrotic hepatitis epithelial cells had disappeared in whole lobules or in large parts of them Remaining cells were vacuolated or acidophilic The framework though itself intact was either entirely collapsed or was still somewhat expanded by erythrocytes Fragments of the pre existing lobules revealed liver cell plates with dense fat free cytoplasm Toward the periphery of the lobules many bile ductules arranged in cords and plate were lined by irregular epithelial cells which sometimes piled up formed giant cells and seemed to be derived from liver cells The lumens of the ductules contained bile casts

In the second type of change the lobular architecture although basically almost always intact was obscured by degeneration and necrosis collapse and regeneration Slits of collapsed parenchyma produced septa linking central zones with each other as well as with portal tracts and dissected portions of the lobules (Fig 82) The isolated portions of the paren hyma exhibited conspicuous regeneration with giant cells and plates of normal dimensions but concentrically arranged

The clinical manifestations were those of diffuse parenchymal liver disease mostly without fever Hepatomegaly was common Sometimes the liver was tender and shrank in the preterminal period

In patients who died the average total dose of iproniazid

The germ count for the H sativum fungi was 89 5 ± 12 2 in the study persons and 114 8 ± 9 6 in the controls whereas for the A tenuis fungi it was 90 5 ± 13 7 and 115 1 ± 10 6 respectively The germ counts in some individual instances did not differ greatly from those obtained among the controls However through discriminatory analysis proper differentiation became possible by using the summary formula $X = x_1 + 0766x_2$ x_1 *standing for the germ count of H sativum* and x_2 for the germ count of A tenuis In persons without a hepatitis history X was 182 and more whereas in those with a definite hepatitis history it was 173 and less The summary formula did not reflect the time which had elapsed since the jaundice nor its severity Nor was there any correlation between the inhibitory effect in the germination test and the results of the protein flocculation reactions (Weltmann s coagulation band Takata Ara reaction cadmium sulfate test) and the bilirubin level of the serum

Serums from patients with active epidemic hepatitis all reacted positively the X values being between 140 and 173 The average of 157 was practically the same as that found among blood donors with a past history of jaundice All serums from patients with infections other than hepatitis gave negative results as did serums from diabetics and cancer patients some of whom had liver metastases

In its present form the germination test is too complicated and unreliable to be of help in clinical medicine or blood bank service

► [This article is refreshing the author presents a type of liver test entirely new to most of us and even after showing that his results are statistically valid he cautions that the test is really too cumbersome and uncertain to be ready for clinical use —Ed]

Pathologic Findings in Jaundice Associated with Iproniazid Therapy are discussed by Hans Popper[4] (Mount Sinai Hosp New York) Iproniazid (Marsilid[®]) phosphate (1 isonicotinyl 2 isopropylhydrazine) an amine oxidase inhibitor has been used in the treatment of tuberculosis and in various mental disorders particularly depressions The author studied liver tissue specimens from 27 patients in whom jaundice developed after they took iproniazid 600 19 200 mg during 4 126 days Pertinent data were available on 16 women and 7 men aged 21 82

Biopsy specimens showed severe spotty hepatitis with or

(4) J.A.M.A. 168 2 35 242 Dec 27 1958

gamma globulin formation under these circumstances are poorly understood There is no evidence that the liver forms gamma globulin but recent observations implicate the spleen and abdominal lymph nodes in gamma globulin elevation in ethionine induced rat cirrhosis

Seymour Glagov Geoffrey Kent (Chicago) and Hans Popper[5] (New York) present an extension of this study to human cirrhosis Of 38 patients studied at autopsy 30 died of diffuse septal or postnecrotic cirrhosis and 8 who were apparently healthy died of gunshot wounds Distribution and morphology of the cells with cytoplasmic pyroninophilia removed by ribonuclease were studied in small pieces of liver spleen bone marrow and lymph nodes (thoracic and abdominal) The technic depends on staining sections with pyronin and comparing them with similar sections stained with pyronin after exposure to digestion with ribonuclease Pyronin stains so controlled by ribonuclease are believed to indicate the presence of ribonucleic acid which in turn is believed to be related to protein synthesis

Several types of pyroninophilic cells resembling primitive reticulum cells lymphoblasts immature lymphocytes immature plasma cells mature plasma cells or lymphocytes were encountered in the lymph nodes and spleen The pyroninophilic cells in the splenic white pulp and in lymphoid follicles did not differ significantly in cirrhosis from those in normals The splenic red pulp and medullary cords of lymph nodes in contrast revealed relatively few usually isolated pyroninophilic cells in normals and a pronounced increase of such cells usually in clusters in cirrhosis Pyroninophilic cells were sometimes noted within foci of inflammatory cells in cirrhotic livers but such foci were not noted in the controls

Pyroninophilia in the lymph nodes and spleen correlated fairly well with preterminal serum gamma globulin levels though there were some exceptions Best correlation was obtained when grading of the lymph nodes and spleen as to the degree of pyroninophilia present was averaged The parallelism between the estimated degree of pyroninophilia and the degree of gamma globulin elevation suggests that excess serum gamma globulin in human cirrhosis is produced at least in part by the lymph nodes and spleen

(5) A M A A h P th 67 9 18 J ry 19 9

average duration of medication and average daily dose per patient were 5672 mg 61 9 days and 1067 mg respectively In most instances iproniazid therapy was discontinued at onset of jaundice In 1 patient who died and 1 who lived therapy was stopped 12 and 20 days respectively before jaundice developed

The syndrome represents a uniform pathologic process of diffuse hepatocellular injury with associated inflammatory



Fig 82—Liver autopsy specimen from patient in whom jaundice developed after intake of proniazid S bacute hepatitis ex ted with subm e collapse acute degeneration (straight ow) and beg ng nodular gen tion and bil t (curved arrow) Hematoxylin-eosin ted ed from × 63 (Courtesy of Popper H J A M A 168 3524 Dec 27 1958)

reaction and bile stasis No morphologic evidence of preexisting liver disease was found in these patients The picture is dissimilar to that usually associated with exposure to chemicals The possible etiologic relation between iproniazid administration and the hepatic lesions may be coincidental or iproniazid may produce a toxic effect indistinguishable from viral hepatitis or iproniazid may activate subclinical viral hepatitis

Relation of Splenic and Lymph Node Changes to Hypergammaglobulinemia in Cirrhosis Elevation of serum gamma globulin accompanies hepatic disease particularly cirrhosis The mechanism of this e [illegible]

gamma globulin formation under these circumstances are poorly understood There is no evidence that the liver forms gamma globulin but recent observations implicate the spleen and abdominal lymph nodes in gamma globulin elevation in ethionine induced rat cirrhosis

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(5) A M A. A h P th. 67 9 18 J ry 19 9

This study throws no light on the contribution of the liver or bone marrow to hypergammaglobulinemia because of the variety of pyronine staining cells encountered in these organs in the material studied

Hyperplasia of Bile Ducts Induced by α Naphthyl Iso Thiocyanate Experimental Biliary Cirrhosis Free from Biliary Obstruction M K McLean and K K Rees[6] (Univ College Hosp Med School London) studied pathologic changes in the rat liver after administration of α naphthyl iso thiocyanate (ANI) a compound capable of inducing bile duct cell proliferation The effects of acute and chronic intoxication were observed

At 12 hours after gastric administration of a single LD_{50} dose of ANI the liver seemed paler than normal A dense inflammatory cell infiltration was centered around the interlobular bile ducts the epithelium of which became swollen From the 2d to the 4th days the liver enlarged and showed small necrotic centrolobular or midzonal areas which were almost free from leukocytic infiltration On the 5th day the inflammatory reaction in the portal tracts was subsiding Fibroblasts grew into the areas of focal necrosis On the 10th day the liver as well as the bile duct epithelium became of normal size and the bile ducts much less prominent From the 12th to the 20th days only a slight increase in periductal fibrous tissue was apparent

During the first 4 weeks of prolonged ANI feeding about 20% of the rats died of generalized toxemia with hepatic failure and jaundice A few days after feeding began the lining cells of the intralobular bile ducts enlarged and divided to form tortuous new ducts which extended centripetally and centrifugally as dense networks of anastomosing channels Later a wilder growth of ducts occurred in which the origin of the cells was not so certain although intralobular duct epithelium still constituted the growing focus New ducts arose as buds of epithelium which extended into spaces between liver cell plates to join up with bile canaliculi and preserve continuity of bile excretion

From 10 days to 3 weeks the inflammation in the portal spaces reached a climax and then started to subside but fibroblasts and bile duct epithelium continued to show extensive hyperplasia By the 6th week the liver became enlarged

(6) J Path & B ct 76 175 188 J ly 1958

with a finely nodular surface After 9 12 weeks bile duct pro liferation was still more advanced and bile thrombi might be found in the ducts At 56 weeks the only macroscopic change was an increase in nodularity Microscopically pseu dolobulation was pronounced

Alterations in the extrahepatic bile ducts were incon tant during prolonged feeding with ANI In the first few weeks the epithelium of tributary ducts was swollen and mitotic division was going on with an increase in small diverticula The common bile duct showed dilated lymphatics and some edema It is felt that ANI induces biliary cirrhosis without obstruction of the bile passages

► [The wide pread use of therapeutic agents that affect the intrahepatic biliary channels and produce hepatitis with intrahepatic chol tasis should stimulate intensive study concerning responsible mechanisms and evolution of the abnormalities produced Unfortunately various laboratory animals do not appear susceptible to such agents as chlorpromazine methyl testosterone and Nilevar® with the result that much uncontrolled speculation particularly with respect to hypersensitivity is prevalent The experiments here cited show that chemically induced lesions of the intrahepatic biliary system of experimental animals can be produced al though the reaction of the liver as a whole appears to be more striking than in patients who suffer an obstructive type jaundice because of expo sure to certain drugs —Ed]

Case of Xanthomatous Biliary Cirrhosis Treated with Ethyl Linoleate is reported by G Walker P F Flynn and L W Kinsell[7] (Highland Alameda County Hosp Oakland Calif) Observations in the authors laboratory that diets rich in polyunsaturated fatty acids lower the plasma total lipid cholesterol and phospholipid levels suggested the trial of large doses of ethyl linoleate in treatment of a patient with primary biliary cirrhosis whose plasma showed characteris tic gross elevation of these lipids

Woman 42 noted insidious onset of tiredness generalized pruritus upper abdominal discomfort and mild jaundice Investigation else where showed that the jaundice wa of the obstructive type Explora tion of the extrahepatic biliary tract showed no abnormality but chole cystectomy was performed Liver biopsy was not taken Symptoms persisted and 1 year later small nontender yellow deposits appeared in the creases of the fingers and palms Within a few months similar lesions involved the skin on all parts of the body Examination re vealed many xanthomas on the hands feet face ears and over the knees and elbow The liver edge was firm and regular and was felt 2 cm below the costal margin Total lipids were 3 900 mg /100 ml total cholesterol 1 490 mg free cholesterol 1 340/100 ml choles terol ester 150 and phospholipids 2 840 mg / 100 ml Plasma bilirubin

(7) La et 1 286 87 F b 7 1959

was 5.8 mg/100 ml mostly direct reacting Liver biopsy showed some periportal fibrosis and dilatation of bile canaliculi

Treatment was started with a 2 200 calorie liquid diet containing 40 Gm ethyl linoleate 97 Gm protein and 362 Gm carbohydrate. Later the ethyl linoleate was increased to 120 Gm. Because this caused diarrhea the dose was decreased to 80 Gm About 2 months after start of treatment the diet was changed to 400 Gm Saf Lac (nonfat milk solids with 40% safflower oil) providing 160 Gm. fat (110 Gm linoleic acid) 84 Gm protein and 124 Gm carbohydrate Fruits vegetables and cereals were added later After treatment for 90 days total lipids had fallen from 3 900 to about 1 000 mg/100 ml During this period total cholesterol fell from 1 490 to 260 mg free cholesterol from 1,340 to 100 mg and phospholipids from 2 840 to 350 mg Cholesterol esters rose slightly from 150 mg/100 ml to 175 mg

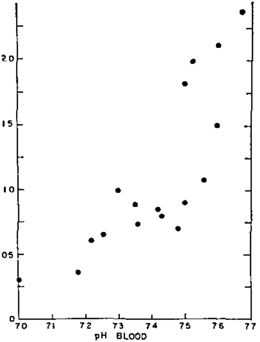
Plasma cholate level was initially about 10 times normal Dihydroxycholate was 35.7 µg/ml (normal mean 3.1) and trihydroxy cholate was 33.6 (normal mean 4.8) After 8 months treatment plasma cholate was still about 7 times normal Plasma bilirubin changed from 6 to 4 mg/100 ml Alkaline phosphatase was 64 King Armstrong units before treatment and 48 after 8 months of treatment (normal mean 8) After 9 months of treatment all but the larger cutaneous xanthomas had disappeared Pruritus became less intense but did not clear completely Subjective improvement was considerable Five months after start of treatment the patient was able to do her housework whereas during the 3 months before admission she had spent most of the time in bed.

Role of pH Gradient in Distribution of Ammonia between Blood and Cerebrospinal Fluid Brain and Muscle was studied by James R Stabenau Kenneth S Warren and David P Rall[8] (Nat l Inst of Health) No direct relationship has been demonstrated consistently between arterial or venous blood ammonia nitrogen concentration or the arteriovenous ammonia nitrogen difference and the state of cerebral dysfunction in hepatic disease In case of a given blood ammonia concentration however the amount of ammonia which may diffuse into the cerebrospinal fluid brain and muscle may be determined by the pH gradient between blood and these other compartments This pH gradient drug distribution hypothesis is essentially that amounts of ionizable compounds existing in two fluid compartments separated by a membrane completely permeable to the unionized species of the compound and relatively impermeable to the ionized species will be distributed unequally when a pH gradient exists between the compartments In the case of ammonia at steady state the greater concentration of total compound

(8) J Clin. Invest 38 373 383 February 1959

should be on the side of the membrane where pH is lower

The authors evaluated distribution of ammonia in the blood to cerebrospinal fluid the brain and muscle of the dog under conditions of experimentally induced pH gradients between the blood and cerebrospinal fluid brain and muscle



F g 83 —R l t n betw blood pH d b d d t b t f mm b to blood (C C) Ob rv 1 C C t t teady t t plotted 1 d dot ga t th pH f blood b rv d d g t dy t t (Co rt y f St ben J R et l J Cl I t 38 373 383 F bru ry 1959)

METHOD —Ammonium bicarbonate solution (0 16N) was infused intravenously in 48 dogs and ammonium chloride (0 16N) into 3 Arterial blood and cerebrospinal fluid pH were determined anaerobically on a Beckman meter Changes in the pH gradients between blood and cerebrospinal fluid during constant ammonia infusion were induced and maintained by intravenous infusion of 0 2N hydrochloric acid intravenous infusion of 0.2N sodium hydroxide Pco elevation and depression by controlled inhalation of a mixture of 20% carbon dioxide and 80% oxygen or of 100% oxygen with carbon dioxide reabsorption

The term C_{CSF} refers to concentration of ammonia in cerebrospi

nal fluid C_M to the concentration in muscle C_{BR} to the concentration in brain and C_{BL} to the concentration in whole arterial blood The distribution ratios of ammonia at steady or near steady state in the various compartments are expressed by C_{CSF} C_{BL}, C_M C_{BL} and C_{BR} C_{BL}.

During metabolic acidosis C_{CSF} C_{BL} decreased significantly to 0 38 from the control infusion value of 0 49 whereas during metabolic alkalosis the ratio increased to 0 85 There was *direct relation between the magnitude and direction of* the pH gradient produced and distribution of ammonia to the cerebrospinal fluid The more alkaline the blood in relation to the cerebrospinal fluid the greater the increase in C_{CSF} C_{BL} Respiratory acidosis and alkalosis did not affect this ratio

The ratio C_M C_{BL} tended to decrease during metabolic and respiratory acidosis and increase significantly during *metabolic and respiratory alkalosis The direct relationship* between increasing blood pH and increasing distribution ratio C_{BR} C_{BL} is illustrated in Figure 83

In hepatic coma knowledge of arterial blood pH is necessary to evaluate the relationship between arterial ammonia concentration and clinical evidences of ammonia toxicity The results explain why *respiratory alkalosis* appears to enhance ammonia toxicity and suggest that corrective therapy utilizing metabolic and respiratory acidosis might be found useful

Effect on Portal Blood Ammonium of Administering Nitrogenous Substances to Patients with Chronic Hepatic Disease was studied by Leslie T Webster Jr Charles S Davidson and George J Gabuzda [9] Nine men and 2 women aged 49 76 who had histories of heavy alcohol and poor dietary intake and physical laboratory and histologic findings consistent with chronic hepatic disease were studied With one exception no patient received foods or medications containing nitrogen for at least 12 hours before the initial blood ammonium determinations were performed Ammonium nitrogen (NH_4 N) was determined by a modified Conway technic in serial blood samples obtained about simultaneously from a superficial abdominal vein an antecubital vein and in some instances an artery usually twice before and at intervals after administration of various nitrogenous substances

Most limitations in assessing fluctuating blood NH_4 N

(9) J Lab & Clin Med 52 501 514 October 1958

concentrations were overcome by comparing concentrations only in blood samples obtained for each patient from the same location in the same abdominal vein on a given day Blood from the superficial abdominal veins was assumed to represent portal blood to some extent Differences between concentrations in two samples of blood drawn at different times during a day from the same site in the same fasting patient ranged from 0 to ± 23 µg /100 ml

Meals containing 20-50 Gm protein consistently increased the portal collateral blood NH_4 N concentrations within 1 hour of consumption Antecubital venous concentrations changed less Oral neomycin did not appreciably alter the increases in abdominal collateral blood NH_4 N produced by protein feeding Intravenous infusions providing 0 8-70 mg /minute urea nitrogen raised the portal collateral and antecubital venous blood NH_4 N concentrations within 15 30 minutes Prior administration of neomycin prevented significant increases in NH_4 N Within an hour of ingestion of l glutamine 3 patients showed significant increases in portal collateral blood NH_4 N concentrations in 3 out of 4 instances Such increases following ingestion of l glutamine occurred despite neomycin administration in 2 patients The amide rather than the amino nitrogen of glutamine seemed responsible for these increase because 10 Gm l glutamic acid given orally as sodium glutamate produced either no change or decreases in portal venous blood NH_4 N concentrations

The maximum amount of volatile base in the nitrogenous substances administered orally was equivalent to about 17 mg NH_4N Significant rises in portal collateral or antecubital venous blood NH_4 N concentrations did not occur when 20 25 mg NH_4 N was given orally to 3 patients on 4 occasions indicating that free NH_4 N in protein or glutamine did not account for changes in collateral venous blood

Although it has been reported that the large intestine is the chief source of portal blood ammonia in animals the interval of 30 minutes in which increases in the portal collateral blood NH_4 N concentration were noted in the patients with chronic hepatic disease suggests that the upper gastrointestinal tract may be an important site of ammonium absorption shortly after protein ingestion in man

The increased portal collateral and arterial blood NH_4 N

nal fluid C_M to the concentration in muscle C_{BR} to the concentration in brain and C_{BL} to the concentration in whole arterial blood. The distribution ratios of ammonia at steady or near steady state in the various compartments are expressed by C_{CSF} C_{BL}, C_M C_{BL} and C_{BR} C_{BL}

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(9) J Lab & Clin Med 52 501 514 October 1958

treatment solution and 500 cc of 5% glucose in water in an identical bottle was used as the control both given intravenously One investigator who did not know the contents of the infusion bottle evaluated results by judging the state of consciousness orientation presence and severity of flapping tremor and ability to calculate and write Basic treatment of hepatic coma was much the same in all

1 Arginine was given 34 times to 31 patients Marked improvement occurred on 2 occasions (5 9%) minimal or moderate improvement was noted 8 times (23 5%) there was no detectable change on 18 occasions (53%) and 6 times (17 6%) the patients definitely worsened On evaluation the next morning 1 of the 2 patients who had shown pronounced improvement maintained it and 1 relapsed Three additional patients who had shown only minimal improvement after arginine infusion appeared considerably improved the next morning

Mean arterial blood ammonium level was 180 μg /100 ml before administration of arginine in the 25 patients in whom it was measured and 160 μg /100 ml after administration The difference between the means is not statistically significant When the study was started arterial rather than venous blood ammonium values were measured in the hope that they would show better correlation with clinical encephalopathy Although there was some correlation it was not a close one

1 Arginine was no more effective than the control solution of 5% glucose in treatment of hepatic encephalopathy

In the human patient with severe liver disease elevated plasma levels of most of the amino acids (including arginine citrulline glutamine and glutamic acid) have been reported Under these circumstances blood ammonium accumulation would logically be ascribed to enzymatic deficiency rather than to lack of substrate and it is not surprising that parenteral amino acid administration is of no value

Ammonia Intoxication Treated by Hemodialysis John E Kiley Joseph C Pender Harold F Welch and C Stuart Welch (Albany Med College) applied hemodialysis to 5 patients who were comatose from ammonia intoxication All had advanced liver disease with ascites and lapsed into coma after massive gastrointestinal hemorrhage All were

(2) New England J Med 259 1156 1161 Dec 11 1958

concentrations noted during intravenous infusions of urea probably resulted from the action of bacterial urease or urea entering the gastrointestinal tract from the blood It is unlikely that urea produced from ingested protein and subsequently broken down in the gut was solely responsible for the portal collateral blood NH_4 N increases which took place after protein ingestion because these increases unlike those occurring during urea infusions were not modified by neomycin administration The failure of neomycin to eradicate the portal collateral blood NH_4 N increases occurring shortly after protein ingestion suggests that treatment with this antibiotic should not replace appropriate protein restriction in management of patients with hepatic coma

► [The results obtained by urea infusion are the basis for another report that endogenous elevation of blood urea caused by renal failure may by similar mechanisms of ammonia production induce signs of hepatic coma in susceptible patients (A M A Arch. Int. Med. 103 15 1959)

In general the meaning of blood ammonia levels continues to be quite puzzling The previous abstract indicated that blood pH and blood-central nervous system gradients may be more important than absolute blood levels in determining the clinical effects of blood ammonia. The increase in ammonium nitrogen here noted by Webster *et al* within 1 hour of protein ingestion and the negligible effect on this increase produced by antibiotic administration are taken by the authors to indicate an intraintestinal mechanism of ammonia production other than bacterial ureases Another explanation however is related to the old problem of whether the methods used really measure blood ammonia. In another report (J Clin Invest. 37 990 1958) blood ammonia is shown to rise more when blood is given by mouth to liver patients than when a nitrogenously equivalent amount of casein or milk solids is given Again the explanation is obscure

The use of blood ammonia levels to evaluate clinical states is also apt to lead to confusion On the basis of experiments here performed Davidson s group concludes that neomycin exhibition should not replace protein restriction in preventing or treating hepatic coma. In an article appearing 3 months later however this group recommends administration of neomycin *with* 30-60 Gm dietary protein (New England J Med 259 1145 Dec. 11 1958) The clinical value of l arginine and dl-ornithine is questioned although blood ammonia levels are less after these agents are given (J Lab & Clin Med 51 672 1958) In this situation evaluation technics such as are described in the next abstract seem to be particularly valuable—Ed]

Controlled Study of Effects of l Arginine on Hepatic Encephalopathy was carried out by T B Reynolds A G Redeker and Paul Davis[1] (Los Angeles) Of the 32 study patients 29 had alcoholic cirrhosis In 23 encephalopathy developed in conjunction with other evidences or progression of their disease such as jaundice and ascites l Arginine hydrochloride 30 Gm in 500 cc distilled water served as the

(1) Am J Med 25 359 367 Sept mbe 1958

tem daily Six received oral potassium supplements of 78 256 mEq daily

A good response with weight loss of at least 2 kg and urinary sodium output increased by more than 39 mEq occurred 9 times In 6 instances response was poor with no weight change and with 1 exception little or no increase in urinary sodium output Five of the patients who were refrac

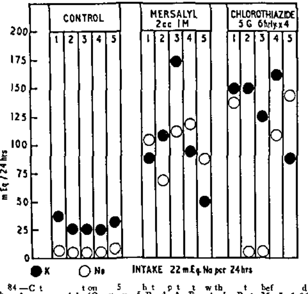


Fig 84—C t t on 5 h t p t t with t bef d ft h d me lyl (Courtesy f R d A E t l B t M J 1 963 966 Ap 26 1958)

tory had a very low initial urinary sodium output (less than 1 mEq daily)

In all patients chlorothiazide resulted in a two to three fold increase in urinary potassium output This resulted in hypokalemia (serum potassium below 3 5 mEq/L) in all 7 patients not receiving potassium supplements In 4 of the 6 receiving supplements the supplements were insufficient to balance urinary loss and serum potassium levels fell The other 2 patients showed poor diuretic response and hypokalemia did not occur

In 5 patients sodium and potassium excreted after 0 5 Gm chlorothiazide every 6 hours for 4 doses was compared with that after 2 ml mersalyl intramuscularly (Fig 84) Mer

treated by esophageal tamponade glutamate administration gastric lavage and catharsis A modified Kolff rotating drum type of artificial kidney was used Removal of ammonia during hemodialysis was calculated by multiplying the flow rate of blood through the artificial kidney by the change in the blood ammonia concentration (measured by the modified Conway technic) during passage through the dialyzer Although this calculation showed ammonia removal clearly it probably did not permit good quantitation of total ammonia removal

CASE 1—In man 57 hemodialysis was carried out for 4 hours 41 L blood was dialyzed and about 71 mg ammonia nitrogen was removed The arterial blood ammonia level had fallen from 250 to 138 µg /100 ml by the end of the dialysis

CASE 2—In man 67 hemodialysis was carried out for 6 hours on 2 consecutive days 36 L blood being dialyzed and about 30 mg ammonia nitrogen removed The only noteworthy change in the blood chemical finding during dialysis was fall in the arterial blood ammonia from 197 to 74 µg /100 ml Seven hours after dialysis venous blood ammonia of 150 µg /100 ml was observed falling to 70 µg /100 ml

CASE 3—In man 49 because of unsatisfactory venous cannulation and subsequent clot formation only 11 L blood was dialyzed and about 8 mg ammonia nitrogen was removed The arterial blood ammonia level was 140 µg /100 ml before dialysis and 150 µg afterward

CASE 4—In woman 43 blood nonprotein nitrogen was 150 mg and creatinine was 6 7 mg /100 ml The venous blood ammonia was 194 µg /100 ml Hemodialysis was carried out for 6 hours 54 L blood was dialyzed about 75 mg ammonia nitrogen was removed and the arterial blood ammonia level changed from 150 to 123 µg /100 ml After dialysis nonprotein nitrogen fell to 55 mg /100 ml

CASE 5—In woman 36 54 L blood was dialyzed and 50 mg ammonia nitrogen was removed with fall of arterial blood ammonia to 70 µg /100 ml and of nonprotein nitrogen from 180 to 100 mg /100 ml

All patients except Case 3 became rational within 12-48 hours of hemodialysis but all 5 succumbed later to their illness or to recurrent hemorrhage Heparinization was not associated with renewed bleeding

► [A simple extracorporeal device for reducing elevated blood ammonia levels is described in a preliminary report (Surgery 44 897 1958) —Ed.]

Chlorothiazide in Control of Ascites in Hepatic Cirrhosis

A F Read R M Haslam J Laidlaw and Sheila Sherlock[3] (Postgrad Med School London) gave chlorothiazide orally 2 Gm daily in 15 courses to 13 patients with Laennec's cirrhosis Patients received a sodium restricted diet (22 mEq) with about 70 mEq potassium and 80 Gm pro

(3) Brit M J 1 963-966 Apr 26 1958

tem daily Six received oral potassium supplements of 78 256 mEq daily

A good response with weight loss of at least 2 kg and urinary sodium output increased by more than 39 mEq occurred 9 times In 6 instances response was poor with no weight change and with 1 exception little or no increase in urinary sodium output Five of the patients who were refrac

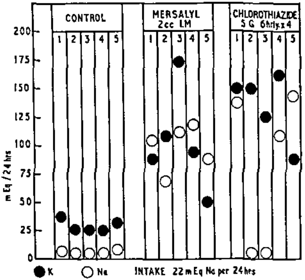


Fig 84—C t t n 5 h t p t t wth t bef d ft hl h d m lyl (C rt y f R d A E et l B t M J 1 963 966 Ap 26 1958)

tory had a very low initial urinary sodium output (less than 1 mEq daily)

In all patients chlorothiazide resulted in a two to three fold increase in urinary potassium output This resulted in hypokalemia (serum potassium below 3 5 mEq /L) in all 7 patients not receiving potassium supplements In 4 of the 6 receiving supplements the supplements were insufficient to balance urinary loss and serum potassium levels fell The other 2 patients showed poor diuretic response and hypokalemia did not occur

In 5 patients sodium and potassium excreted after 0 5 Gm chlorothiazide every 6 hours for 4 doses was compared with that after 2 ml mersalyl intramuscularly (Fig 84) Mer

salyl increased sodium excretion in all and chlorothiazide increased it in 3 Potassium excretion after mersalyl was lower than sodium loss in 3 patients but after chlorothiazide potassium excretion was lower in only 1

Hepatic precoma or coma was noted in 7 of the 13 patients treated with chlorothiazide The EEG proved the most sensitive record of impending neuropsychiatric disturbance but major electric abnormalities were always accompanied by clinical evidence of precoma All patients with evidence of precoma or coma had a past history of precoma Chlorothiazide should be given with extreme caution if such history is elicited or if neuropsychiatric abnormalities can be detected

The mechanism of hepatic coma is uncertain Chlorothiazide in vitro has carbonic anhydrase inhibitor properties which is confirmed by the finding of increased urinary excretion of bicarbonate and an accompanying rise in urinary pH after its administration The carbonic anhydrase inhibitor acetazolamide induces hepatic precoma in some patients with liver disease by blockage in uptake of ammonium by peripheral tissues Chlorothiazide might act similarly though perhaps with less potency

Correlation was noted between the extent of diuresis and development of precoma possibly because of alterations of osmolarity and loss of electrolytes Potassium loss may be of particular importance Unfortunately therapy is particularly dangerous in the group having the most satisfactory diuresis

► [An essentially similar report may be found in the *New England Journal of Medicine* (259 1151 Dec 11 1958) —Ed]

Hazards Attending Use of Esophageal Tamponade Harold O Conn[4] (Yale Univ) analyzed data on 50 patients in whom the Sengstaken Blakemore tube was used Average intubation period was 78 hours and the range was 10 minutes to 12 days Major complications developed in 19 patients and were fatal in 9 Potentially fatal errors occurred during 55 of the 81 episodes of esophageal tamponade Erosions of the pharynx and esophagus were noted in 17 of 31 patients at autopsy Lacerations of the esophageal mucosa similar to those of the Mallory Weiss syndrome appeared as a result of esophageal tamponade in 3 patients Each of these died in severe respiratory distress Traumatic rupture of the esophagus occurred

(4) New England J Med 259 01 707 Oct 9 1958

in 1 patient who presumably had bled from peptic esophagitis Bleeding had been intermittently controlled by recurrent use of the tube over 8 days

Obstruction of the airway which is the most serious complication was responsible for 9 deaths In 8 it was caused by regurgitation of blood or bloody gastric contents with occlusion of air passages Regurgitation was most commonly precipitated by manipulation or passage of the tube or by suctioning of the pharyngeal space In several patients regurgitation followed rupture of the gastric balloon Occlusion of the airway may also be caused by the distended esophageal balloon when the gastric balloon no longer anchors the tube in place This occurred in 4 patients and caused death by asphyxiation in 1 Improper use of the Sengstaken Blakemore tube can be attributed chiefly to inexperience and inattention The occasional finding of medications within the gastric or esophageal balloon attests to the accidental release of pressure Mechanical defects of the Sengstaken Blakemore tube are a common cause of trouble

Diagnostic errors may be made if the tube is used to differentiate variceal bleeding from other causes of upper gastrointestinal hemorrhage As noted at autopsy 6 patients had bled from peptic ulcers of the stomach or small intestine Hemorrhage appeared to have been adequately controlled by the tube in 5 as evidenced by the decreasing blood content of the gastric aspirations and stability of the vital signs

To prevent complications a new tube should always be used the balloons must be checked for leaks and asymmetry the gastric contents must be aspirated immediately the gastric balloon is inflated with 200 250 ml air the tube must be fixed by taping a cube of sponge rubber to the tube at the nasal orifice not by using elastic bands or weights to maintain traction the esophageal balloon is inflated to a pressure of 40 mm Hg nothing must be administered orally and nursing attendance must be constant

► [In some quarters the use of balloon tamponade to control bleeding from esophageal varices is being viewed with increased skepticism patients die just the same despite apparent temporary control of the bleeding and such difficulties as here described would suggest that balloon tamponade may be not only useless but actually hazardous By others however this therapeutic techn c continues to be highly regarded One reason for the difference in opinions concerning the efficacy of esophageal balloon tamponade must depend on the factors here detailed by Conn. If an experienced phys cian and nursing team are constantly on duty watch

ing and testing the balloon and insuring its adequate function results are obviously better than if the balloon tube is tended by inexperienced personnel harried by the multitudinous duties of a house officer or ward nurse The question of course arises whether meticulous and specialized care by doctors and nurses of patients with bleeding esophageal varices would not be as effective without a Sengstaken Blakemore tube as with it. An adequately controlled study on this question is not yet available —Ed.]

Treatment of Cirrhotic Ascites by Combined Hepatic and Portal Decompression was studied by William V McDermott Jr[5] (Harvard Med School) Experimental ascites can be easily produced by any procedure that obstructs outflow from the liver and transudation from the liver itself accounts for a major portion of the accumulated fluid In cir

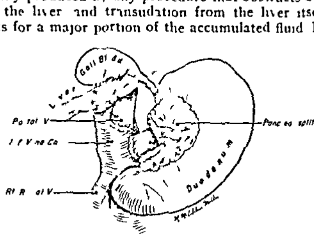


Fig 85 —Operat e p oc d e d scr bed a doubl port ca l b t wh ch mpl sh s po tal d h pat dec mpres n (Courte y f McD rmott W V Jr N w E gl nd J Med 259 897 901 N 6 1958)

rhotic ascites in man intrahepatic outflow block arterio portal communications increased intrahepatic pressure and increased transudation of hepatic lymph constitute a similar mechanism for ascites production although osmotic pressure relations are also important Since there is abnormal retention of sodium and water and salt restriction often brings about amelioration of the ascitic accumulation increased aldosterone activity is evident in these patients This hyperaldosteronism however is believed to be secondary to loss of sodium and water into the peritoneal cavity rather than the cause of total increase of sodium and water in the body

Based on the concept that intrahepatic outflow block is a major physiologic disorder in cirrhotic ascites the author treated 6 patients with intractable cirrhotic ascites by com

(5) New E gl d J Med 259 897 901 N v 6 1958

bined portal and hepatic decompression (Fig 85) Results were excellent

Man 43 had been a moderately heavy drinker for 10 years His abdominal girth had been increasing for about a year Despite abstaining from alcohol a well balanced diet rigorous sodium restriction (200 mg daily) added potassium chloride and treatment with mercurial diuretics neither change in weight of girth nor evidence of diuresis ensued Several paracenteses helped only temporarily

At surgery portal pressure was equivalent to 31 cm saline solution After occlusion of the portal vein pressure on the intestinal side rose to 37 cm and that on the hepatic side fell to 24 cm saline solution The ascite was dissipated by laparotomy but during follow up of over a year fluid has not reaccumulated within the peritoneal cavity despite unrestricted salt intake and absence of specific treatment Bromsulfalein retention in 45 minutes 23% before surgery fell to 17% in 5 months after surgery On the 3d postoperative day sodium began to appear in the urine in appreciable amounts

The double shunt procedure should decompress the liver but it remains to be seen whether the theoretical advantages of the double shunt will compensate for the increased technical difficulties as compared with the side to side portacaval shunt

► [In a personal communication (June 1959) Dr McDermott reports that he has performed 12 double shunt procedures on patients with portal hypertension and ascites Ten survived the early postoperative period and of these 8 have been successful to the point that ascites has not reaccumulated even though dietary salt has been permitted —Ed]

Critical Evaluation of Venous Shunts for Treatment of Cirrhotic Patients with Esophageal Varices is presented by Marvin M Nachlas[6] (Johns Hopkins Univ) Reports on shunt surgery are inconclusive because too few cases are reported follow ups are too short patients with extrahepatic obstruction are included among those having liver disease proof that the varices were the cause of hemorrhage is occasionally lacking and patients with varices who have never sustained a hemorrhage are included in some series

Although at least 60% of cirrhotic patients have varices only 25% sustain serious hemorrhage and the susceptibility to hemorrhage cannot be correlated with portal pressure Some patients who have not bled have had higher portal pressures than others who did bleed pressures in large varices may be lower than those in small ones and some patients have repeated and severe hemorrhages with normal or only slightly elevated portal pressures Though the pressure in the distal part of the portal system (hemorrhoidal veins)

(6) \ S g 148 169 183 A gu t 19 8

rises to over 600 mm water when the patient is erect massive hemorrhages do not occur from undiseased bowel in this area

On the basis of reported observations the success of portal systemic shunts is far from bright In most clinics it is not possible to perform a venous shunt in 1 patient of every 4 in who it is attempted The mortality rate of the operation although variously reported averages around 18% In surviving patients a well constructed venous shunt may appreciably reduce portal pressure but only relatively minor reduction in portal pressures has been reported in a significant number of patients After shunt operations a recurrence rate of about 20% has been reported for hemorrhages and all of these cannot be attributed to occlusion of the venous anastomosis Finally combined experiences reveal that only 40% of patients are free from varices after venous shunts have been created

Portal systemic shunts in addition may be harmful in that beneficial collaterals will be interrupted during operation hepatic blood flow will be reduced and in particular the patient may be exposed to cerebral ammonia intoxication

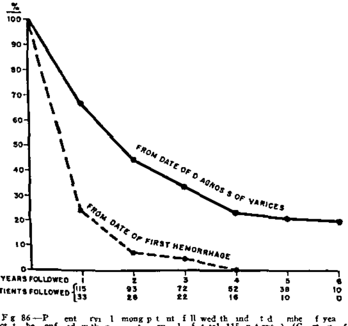
Of 200 patients with cirrhosis of the liver who bleed from varices only 100 will survive the initial hemorrhage For illustrative purposes 50 of these patients may be supposed to be treated medically and 50 to be considered for surgical treatment Five of the surgical group will be denied portal decompression because of poor liver function Nine of the 45 patients operated on will have operative deaths leaving 36 patients who survive the venous shunt operation Four of these survivors will die within 1 year Thus 32 patients of the entire group will successfully undergo portal decompression and live more than 1 year This end result does not differ significantly from that expected for the 50 medically treated patients

The abundant evidence which raises doubts as to the value of the venous shunt operation should counteract the recent trend to extend the shunt operation to patients with varices who have never bled

Natural History of Esophageal Varices *Study of 115 Cirrhotic Patients in Whom Varices were Diagnosed Prior to Bleeding* is presented by Lyle A Baker Clifford Smith and

Gerald Lieberman[7] (VA Hosp Hines Ill) The clinical course uninterrupted by surgery is analyzed in patients in whom diagnosis was established by esophagoscopy Follow up was at least 1 year in 22 patients 2 years in 93 3 years in 72 4 years in 52 5 years in 38 and 6 years in 10

Of the 115 patients bleeding occurred in 33 (28 6%) In 23 the first hemorrhage occurred within 1 year of diagnosis and in 30 patients within 2 years This suggests that in patients who survive 1 year or more with no bleeding after diagnosis of varices the chances of hemorrhage are small



F g 86—P ent rvi l mong p t nt f ll wed th ind t d mbe f yea (Not t be onf ed w th p t rv l f t tal 115 p t ent) (C rt y f B k L. A *et l* Am J M d 26 8 237 F bru ry 1959)

Within the study period 74 patients died 20 (17 3%) due to exsanguination 31 (26%) of hepatic failure and 23 (20%) of unrelated causes Of particular importance is the fact that 11 (9 5%) died of the first hemorrhage The survival curve (Fig 86) emphasizes the critical nature of the first 2 years after diagnosis of varices Comparison of the two curves in

(7) Am J M d 2 228 37 F bru y 1959

Figure 86 indicates the fallacy of extending the extremely poor prognosis of patients with esophageal varices that have bled to patients with esophageal varices diagnosed before bleeding. Only one third of the latter group died in the 1st year compared with three fourths of the former group. To assume that patients with latent varices are inevitably doomed to bleed and necessarily have a poor prognosis is an erroneous basis for recommending routine prophylactic shunt surgery.

Hemorrhage occurred nearly twice as often among patients with large varices as among those with small or moderate sized ones. However, mortality from the first hemorrhage was inversely proportional to the extent of the varices. Only 1 of 11 patients with large varices died of the first hemorrhage, whereas 8 of 13 with small ones died.

The objective of routine prophylactic shunt surgery for nonbleeding esophageal varices is directed toward preventing mortality from the first hemorrhage. On the basis of the findings in the present group it is estimated that by the time all 115 patients are dead 10-15% will have died of the first hemorrhage. This, then, is the ultimate possible goal of achievement against which must be balanced the mortality, failures and complications of routine prophylactic decompression surgery. At present, routine surgery does not offer definite advantage to the patient.

Use of Intravenous Pituitrin® in Treatment of Bleeding Esophageal Varices is described by Seymour I. Schwartz, Harold W. Bales, George L. Emerson and Earle B. Mahoney[8] (Univ. of Rochester). The direct effect of intravenous surgical Pituitrin® on portal venous pressure was investigated in 9 patients during operation for portacaval or splenorenal anastomosis. After intravenous administration of 20 clinical units of the drug, the portal pressure in 8 patients fell from about 300-400 mm. H_2O to 100-300 mm. within 15 minutes. The portal pressure was reduced by Pituitrin® to the same level that resulted from a subsequent shunt. In 1 patient, portal pressure remained unchanged.

In 9 patients with esophageal varices, 25 episodes of acute bleeding were treated by intravenous injection of 20 units of surgical Pituitrin® or Pitressin®, usually diluted with 200 cc. of 5% dextrose in distilled water and given over a half

(8) S. g. y. 45:72-80, Ja. ry 1959

hour In 22 episodes bleeding was promptly controlled In 2 other patients who were initially treated by Sengstaken Blakemore tube without control of bleeding addition of intravenously administered Pituitrin® brought about prompt cessation of hemorrhage

On two occasions intravenous Pituitrin® was used to facilitate transesophageal ligation of bleeding varices Transthoracic esophagotomy resulted in brisk bleeding that obscured the surgical field Dramatic reduction in bleeding followed use of 20 units of Pituitrin® over 3 minutes

In intravenous administration of Pituitrin® rapid infusion is necessitated by the tachyphylactic property of the drug Therapy can be repeated at 4-hour intervals if bleeding continues or recurs Pituitrin® and Pitressin® when given intramuscularly are ineffective in the control of bleeding Arterial pressure should be checked very 5 minutes while Pituitrin® is being given intravenously and the rate of infusion should be slowed if marked elevation of blood pressure occurs

► [As Dr Robert Linton said in discussing this method It almost sounds too simple Control studies and ultimate mortality figures are lacking and it should be noted that gastric suction was also used in treating the 9 patients with esophageal bleeding Perhaps most discouraging is the fact that 9 patients had to be treated 25 times for repetitive bleeding episodes! Nevertheless any method that helps stem the flow of blood from a ruptured esophageal varix is valuable even if the benefit is temporary —Ed.]

Comparative Study of Various Mechanisms of Hepatic Restoration in the Rat With the advent of extensive hepatic resection it has become apparent that the human liver like that of laboratory animals restores itself after major resection by an increase in size of the remaining liver Most investigators favor an increase in portal flow through the remaining lobes as the causative mechanism for the impressive restoration It has been suggested that the regenerative process that occurs after partial resection of the liver might be used in patients with cirrhosis If the growth of new liver is due to changes in portal flow occlusion of a major tributary of the portal inflow to the liver should produce the same result as removal of the liver supplied by this portal branch

Walter Lawrence Jr Daniel Joly and Richard Brasfield[9] (New York) studied the degree of liver restoration in 230 fe

(9) S [illegible] 45 543 551 [illegible] 1959

male Wistar rats that survived these surgical procedures to the left lateral and median lobes of the liver (1) excision with removal of 65 70% of the liver mass (2) ligation of the hepatic duct draining the lobes (3) ligation of the portal blood supply to the lobes and (4) occlusion of both arterial and portal blood supply Two thirds of the animals were killed after 4 weeks and the others after 8 weeks

The final liver weight in all groups closely approximated the expected liver weight of the normal rat Rats subjected to hepatic duct ligation had minimal atrophy of the corre sponding lobes and little increase in the rest of the liver There was a marked effort to restore liver after partial liver removal and almost as intense restorative response occurred in rats with all vascular supply to a portion of the liver oc cluded Ligating only the portal blood supply produced marked atrophy of the corresponding liver lobes and definite increase in size of the remaining liver There was however significantly less hypertrophy than in the group subjected to removal of lobes

The clinical trial of hepatic duct ligation in cirrhotic pa tients to produce liver growth stimulation seems unwar ranted but attempts to induce hypertrophy of liver by liga tion of a portion of the portal flow seem worthy of further investigation This study also suggests that hypertrophy of residual liver after partial hepatectomy in rats cannot be at tributed entirely to increase in portal flow or pressure

► [There is something fishy in this suggestion that attempts be made to induce hypertrophy of the human cirrhotic liver by ligating or occluding some of its portal blood supply Is not portal blood flow already grossly deficient? Does normal hypertrophy follow a portacaval shunt proce dure? It is thus questionable whether these results obtain d in normal rats can be applied to the cirrhotic liver of man where the dynamics of intra hepatic arterial and portal flow are already so grossly altered

The next abstract however would seem to indicate that in rats at least ablation of a section of liver made abnormal by carbon tetrachloride is followed by regeneration of es entially normal tissue!—Ed]

Regenerative Hyperplasia of Cirrhotic Liver Following Partial Hepatectomy Abdol H Islami George T Pack and John Castleman Hubbard[1] studied the effects of partial hepatectomy in rats with the liver rendered cirrhotic by ex perimental methods After the right lobe which comprises 60% of the weight of the human liver is excised the impulse for liver regeneration is initiated in the left lobe The in creased bulk of the left lobe is due to true proliferation of new

(1) Ca c r 11 663 686 J ly A g 1958

liver tissue Chemical analyses of aliquots of the regenerated liver show values identical with those of the normal liver Nuclear counts of homogenized residual liver tissue in the rat and dog confirm the tenet that the increased liver sub stance is due to true regenerative hyperplasia The rapidity of liver regeneration after subtotal hepatectomy appears to be inversely proportional to the size of the animal

METHOD—The rats in group 1 were maintained as normal growth controls Those in groups 2 and 3 were given on alternate days in tramuscular injections of a solution containing by volume 10% car bon tetrachloride and 90% olive oil Group 2 received a total of 15 cc carbon tetrachloride solution and group 3 received 54 cc in all In group 2 70 % partial hepatectomy was carried out in 15 rats 30 days after the first of the 15 injections of carbon tetrachloride and in 12 in group 3 90 days after the first of 45 injections

Growing rats with advanced carbon tetrachloride pro duced cirrhosis accompanied by massive ascites could com pletely recover from the cirrhosis by regeneration of essen tially normal liver tissue arising from the residual cirrhotic liver after 70% partial hepatectomy The nonoperative con trols with advanced cirrhosis during the same time and in absence of further administration of carbon tetrachloride showed microscopically some regression of cirrhosis but had large collections of ascitic fluid severe growth retardation and some loss of body mass

Of the 8 partially hepatectomized survivors 6 were killed 1 month after the 70% partial hepatectomy At this time the mass of the regenerating and residual livers averaged 10 9 Gm The livers were smoother but retained some evidence of previously accentuated granularity

Two rats in group 3 were killed 3 months postopera tively these had no ascites and the liver weight was 13 6 and 13 95 Gm with normal color and texture smooth surface and disappearance of fibrosis The livers in nonoperated con trols weighed 10 10 and 10 12 Gm and were markedly fibrotic

Because of the markedly similar vascular architectural dis tortions in the final patterns of well established human por tal cirrhosis and in the carbon tetrachloride produced cir rhosis in rats a study of the possible applicability of massive partial hepatectomy as a technic for the treatment of human cirrhosis is a realistic and promising goal

One Stage Homotransplantation of Liver Following Total Hepatectomy in Dogs is described by Francis D Moore Louis L Smith Thomas K Burnap Frederick D Dallenbach Gustave J Dammin Ulrich F Gruber William C Shoemaker Richard W Steenburg Margaret R Ball and John S Belko (Peter Bent Brigham Hosp Boston)

METHOD—Donor dogs were operated on at normal body temperature but the liver was subjected to regional hypothermia by introducing chilled sterile salt solution into the peritoneal cavity The blood supply was occluded and the liver transferred when its temperature was about 28 C After splenectomy in the host dog the liver was removed and the cold donor liver sutured in place Four vascular anastomoses are required the inferior vena cava below the liver and above the diaphragm portal vein and hepatic artery Biliary drainage was re established by cholecystenterostomy or cholecystostomy The cold transplant rewarms gradually as blood flow is re-established in the recipient Vascular homeostasis was maintained during transplantation by two low pressure shunt systems one from the inferior vena cava to the jugular vein low in the neck and the other from the portal vein to the opposite jugular vein The shunts were removed after completion of transplantation Fresh blood transfusions were given as needed during and immediately after surgery blood collected within 30 60 minutes of its administration being used to prevent bleeding due to hypofibrinogenemia

The longest survivals after homotransplantation of the liver have been 5 and 6 days during which periods the transplanted liver has shown unquestionable evidences of function One animal died of cerebral embolus with continuing evidence of good liver function The other died after rapid appearance of jaundice with sudden hepatic failure

Maintenance of normal hepatic functions was evidenced by normal serum albumin concentration and an intact coagulation mechanism Platelet counts were normal with normal concentrations of fibrinogen and prothrombin and normal clotting times Blood urea sugar pH and electrolytes were normal Bile production continued and serum bilirubin concentration and cholesterol esters remained normal rising only terminally in the dog showing acute liver failure

In both dogs pathologic examination revealed a mononuclear infiltration in the transplanted livers with predilection for a perivascular distribution resembling that described in other homotransplanted organs There were also foci of necrosis canalicular bile stasis and arteritis

► [Following the success achieved by the Peter Bent Brigham Hospital group in homo ransplantation of human kidney this same group is show

(2) Tra spla t Bull 3 103 106 J u y 1959

ing that the transplantation of other vital organs is technically feasible although exacting If homograft rejection by recipient antibody formation can be controlled the possibilities of organ homotransplantation appear limitless

In the future perhaps we shall not try to stimulate regeneration of normal liver by merely cutting chunks off a cirrhotic organ we will merely give the patient an entirely new liver i e is someone is willing to part with his —Ed.]

Hepatic Amebiasis Study of 250 Cases N McE Lamont and N R Pooler[3] (Univ of Natal) included in their studies only patients who presented at least three of the following criteria for the diagnosis of amebic liver disease tender enlargement of the liver response to specific antiamebic therapy suggestive hematologic and/or x ray finding and the demonstration of pus by aspiration or by rupture into an adjacent viscus or serous cavity

All 250 patients had an enlarged and tender liver These features are probably the result not of a diffuse amebic hepatitis but of vascular congestion accompanying amebic abscess formation The tenderness in hepatic amebiasis may be very intense compared with that encountered in other causes of hepatomegaly and in general tenderness is greatest when enlargement of the liver is rapidly progressive The more generalized the pain and tenderness the greater was the likelihood of finding pus on aspiration

Treatment apart from procedures such as aspiration and surgical drainage consisted of a 10 day course of emetine (1 gr daily) together with or followed by a 3 week course of chloroquine (1 gr daily for 2 days followed by ½ gr daily) Occasionally antibiotics were used in the complicated cases Sixteen (6 4%) patients died 154 responded rapidly and 80 slowly When pus is abundant a slow response to specific therapy may be expected for all those with slow responses had undisputed abscesses An abscess can however resolve without aspiration Thus cases diagnosed as nonsuppurative amebic liver disease may in fact be instances of small deep seated abscesses which resolve on therapy

Anemia in amebic liver disease is usually normocytic and normochromic with mild anisocytosis and polychromasia In 18% the white blood cell count was below 9 000 in 35% it was between 9 000 and 15 000 in 37% it ranged between 15 000 and 25 000 and in 9 5% it was over 25 000 The white blood cell count was not a reliable criterion for distinguish

(3) Quart J Med 27 389-41 July 1958

ing between pyogenic and amebic liver abscess The longer the illness lasted the greater was the chance of a normal count Serum bilirubin was over 0 8 mg /100 ml in 19 of 187 patients Liver function tests though not diagnostic may be of prognostic help

X rays detected abnormalities in 84% of patients so examined The right diaphragm was elevated in 65% a pleural reaction with effusion appeared in 35% and less frequent findings were linear atelectasis and lower lobe consolidation The absence of radiologic abnormalities in hepatic amebiasis suggests intraperitoneal encroachment An abscess of the left lobe in particular may not become evident until it is about to rupture into the thoracic cage

In 136 (54%) pus in the liver was demonstrated by aspiration or by rupture The abscess ruptured in 44 patients in 21 into the right and in 12 into the left pleural cavity in 10 into the peritoneal cavity and in 1 into the colon Intraperitoneal rupture was characterized by acute abdominal pain shock free fluid and recession of the liver edge The long term effects of amebic liver pus within the peritoneal cavity seemed fairly innocuous Of 17 patients with intrapulmonary rupture 16 recovered Of 9 patients with intrapleural rupture 8 recovered Amebic involvement of the pericardium occurred in 7 patients 2 lived

Pus was aspirated from the liver in 106 patients The pus was frankly purulent in 36 anchovy in 43 and mixed with blood in 27 The only reaction was relief In the presence of a large abscess the possibility of other abscesses must not be ignored

Biopsies from amebic livers with abscesses showed only small scattered microscopic foci of colliquative liver cell necrosis not resembling viral hepatitis A pathologic basis for amebic hepatitis does not exist It is believed that the earliest phase of amebic liver disease is a focal lesion which may be a silent hepatolytic process not evoking clinical attention until it has progressed to a larger abscess

Evaluation of Hemagglutination and Flocculation Tests in Diagnosis of Echinococcus Disease Echinococcosis of the liver lungs and central nervous system is associated with presence of a circulating antibody in the patient s serum Serologic diagnosis has been based chiefly on results of the Casoni skin test and complement fixation test Sensitivity

of the skin test varies from 53 8 to 100% and a positive test may indicate only previous exposure rather than recent infection The complement fixation test has limited sensitivity variously reported as 52 4 82%

Irving G Kagan Dorothy S Allain and Lois Norman[4] (USPHS Atlanta Ga) evaluated Boyden s tannic acid hemagglutination test and a bentonite flocculation test for detecting echinococcus disease in serums from 30 clinically diagnosed patients Sensitivity of the tests was evaluated with 246 serums from nonechinococcus patients including 124 with protozoan helminthic treponemal and mycotic diseases The antigen used in both tests and in complement fixation tests was pig hydatid fluid that was dialyzed for 24 hours in running water and concentrated threefold by per evaporation

Boyden s test consisted of determining the degree of agglutination produced when serum was added to sheep erythrocytes that had been treated by exposure to tannic acid hydatid fluid antigen and normal rabbit serum In the bentonite test the degree of flocculation was read after the test serum had been added to bentonite particles 1 2 μ in size and coated with hydatid fluid antigen

The hemagglutination test was positive for 29 of 30 serums from clinical echinococcus infections The bentonite flocculation test was slightly less sensitive giving 27 positive results In titration of 246 nonechinococcus serums 14 2% gave false positive results with the hemagglutination test In most instances titers were 1 50 or 1 100 With the bentonite flocculation test 10 1% of serums showed false positive results The complement fixation test was positive in only 36 3% of 22 serums from patients with active echinococcosis but showed no cross reactions with nonechinococcus serum Attempts to increase sensitivity of the complement fixation test resulted in anticomplementary serum

On the basis of the limited data so far obtained the authors feel that in serum submitted for diagnosis of echinococcosis a titer of 1 200 or higher in the hemagglutination test and positive bentonite flocculation test of 1 5 or greater may be considered presumptive evidence of active infection with this disease Serum with low hemagglutination titer (1 50 or 1 100) and negative bentonite flocculation titer or the

(4) Am J T p M d. 8 51 55 J ary 1959

reverse low bentonite flocculation titer and negative hemagglutination titer may reflect nonspecific serologic responses Until more proved positive serums can be tested with the hemagglutination and bentonite flocculation tests it is advisable to test all unknown serums with both procedures

Biologic Studies of Dihydrocholesterol IV Effect of Bile Acids and Other Choleretic Agents on Dihydrocholesterol Induced Cholelithiasis in the Rabbit was investigated by Erwin H Mosbach Margaret Bevans Ruth Kaplan Evelyn Halpern and Don Harris[5] (*Columbia Univ*) Of 18 rabbits fed 0 5% dihydrocholesterol for 4 weeks 17 had gallstones The gallbladders in these animals showed congestion and thickening of the walls as previously reported In about half the animals the intra and extrahepatic ducts contained concrements Of 10 rabbits given 0 5% dihydrocholesterol plus 0 25% dehydrocholic acid for 4 weeks 8 had no gallstones

Hyodesoxycholic acid and the nonbile acid choleretics *Zanchol® MA C2 and Gallogen® were ineffective in suppressing* gallstone formation and inflammation of the gall bladder In contrast desoxycholic acid and cholic acid completely prevented dihydrocholesterol induced cholelithiasis and suppressed development of inflammatory lesions Of 6 animals receiving Dreole (p hydroxyphenylsalicylamide) plus dihydrocholesterol only 4 had gallstones Weight of the stones and over all *pathologic involvement* were distinctly diminished compared with controls receiving dihydrocholesterol alone

The present investigation confirmed results of earlier studies *indicating* that *concentration of dihydrocholesterol* in the tissues bears no simple relation to intensity of the lesions produced in the biliary tract Though animals receiving desoxycholic acid plus dihydrocholesterol had serum and liver sterol concentrations that were much higher than those found in any other group they had no biliary calculi and showed minimal inflammation of the biliary tract This finding suggests two possible explanations for the absence of biliary calculi in rabbits receiving dihydrocholesterol plus cholic desoxycholic or dehydrocholic acids administration of bile acids inhibits conversion of sterols to cholanic acids by the liver or desoxycholic cholic and dehydrocholic acids are more effective choleretic agents than

(5) A M A A ch P th 67 197 203 F bru y 1959

the other substances studied If the second explanation is found valid dihydrocholesterol fed rabbits would prove useful for evaluating choleretic drugs

Incidence of Gallbladder Disease in Normal Men Richard S Wilbur and Robert J Bolt[6] (Univ of Michigan) analyzed results of routine cholecystograms performed in the course of annual physical examinations of 1 233 male executives All were working and may be considered repre sentative of men in the actively productive years Average age was 46 8 and most were aged 35 55 Cholecystograms were done with 2 Gm Telepaque® given the night before examination

Some abnormalities were present in 182 (14 6%) (table)

CHOLECYSTOGRAM FINDINGS IN 1 233 NORMAL MEN

C g ry	Numb	P C t	A erag Ag
Normal cholecyst g am	1051	85 4	46 ?6
Post hole ystect my	25	2 0	51
Fa nt vis al zat n	45	3 6	50 6
N nvisu l zat n	0	1 6	51 6
B l a y lcul	9?	7 5	48 3
Total abnorm l	18	14 6	49 9

These included previous cholecystectomy 2% faint visuali zation 3 6% nonvisualization 1 6% and biliary calculi 7 5% Though in most categories the men with abnormal x rays had more symptoms than those with normal films the incidence of complaints was significant (58%) only n the nonvisualization group Of the men with tones 70% were asymptomatic as were 86% in a control group con sisting of the first 488 persons having no gallbladder ab normality Only 16% of the men with stones had symptoms suggestive of gallbladder disease whereas 14% had vague indigestion Of the controls 4 5% had vague indigestion and 10% had symptoms that might cause a physician to suspect gallbladder disease—epigastric pain biliary colic history of jaundice nausea and/or vomiting

Among the postcholecystectomy patients after eliminat ing those with known associated diseases 5 (31%) still had indigestion epigastric pain or both—the same symptoms

(6) G t t l gy 36 251 55 F bru ry 1959

reverse low bentonite flocculation titer and negative hemagglutination titer may reflect nonspecific serologic responses Until more proved positive serums can be tested with the hemagglutination and bentonite flocculation tests it is advisable to test all unknown *serums with both procedures*

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(5) A M A Arch P th 67 197 203 F b ary 1959

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Some abnormalities were present in 182 (14.6%) (table).

CHOLECYSTOGRAM FINDINGS IN 1,233 NORMAL MEN

Category	Number	Per Cent	Average Age
Normal cholecystogram	1051	85.4	46.6
Postcholecystectomy	25	0	51
Faint visualization	45	3.6	50.6
Nonvisualization	20	1.6	51.6
Biliary calculi	92	7.5	48.3
Total abnormal	182	14.6	49.9

These included previous cholecystectomy 2%, faint visualization 3.6%, nonvisualization 1.6% and biliary calculi 7.5%. Though in most categories the men with abnormal x-rays had more symptoms than those with normal films, the incidence of complaints was significant (58%) only in the nonvisualization group. Of the men with stones, 70% were asymptomatic, as were 86% in a control group consisting of the first 488 persons having no gallbladder abnormality. Only 16% of the men with stones had symptoms suggestive of gallbladder disease, whereas 14% had vague indigestion. Of the controls, 4.5% had vague indigestion and 10% had symptoms that might cause a physician to suspect gallbladder disease—epigastric pain, biliary colic, history of jaundice, nausea and/or vomiting.

Among the postcholecystectomy patients, after eliminating those with known associated diseases, 5 (31%) still had indigestion, epigastric pain or both—the same symptoms

(6) G[illegible] t[illegible] ert [illegible] 1 [illegible] Ry 36 251-255 F[illegible] bru[illegible] ry 1959

that prompted surgery initially Thus the percentage of patients with gallbladder symptoms in this group was almost identical with the percentage (30%) in the group who still had stones Typical biliary colic was a symptom in 4 (0 9%) *controls and in only 3 (3 6%)* patients *with proved* stones

Judging from the results of this survey the number of active American men with asymptomatic gallstones must be in the millions Incidence of gallstones in men rises sharply after retirement age and the percentage in women is significantly higher until the 7th decade The attempt to eradicate all these gallstones would seem to be enormous and unrewarding though it has been advocated strenuously

► [Here s how you can annoy your surgical colleague especially after he has insisted that your patient with asymptomatic gallstone should have prophylactic cholecystectomy for fear of the consequences that befall those who have their tones left in place The first thing you ask him after he has stopped expounding is whether he has had a Graham test in the past year Unless he has had biliary tract symptoms the chances are overwhelming that he has not On getting this information you look worried and somewhat horrified. After all assuming that your surgical friend is more than 48 years old (see table) he has 1 chance in 10 of having asymptomatic gallstones and if he *really* believes that this is such a threatening condition, he certainly should have a cholecystogram about once every 5 years just to make sure —Ed.]

Common Bile Duct after Cholecystectomy In 73 patients undergoing cholecystectomy L P Le Quesne C G Whiteside and B H Hand[7] (Middlesex Hosp London) measured the diameter of the common bile duct as revealed on operative cholangiography and on intravenous cholangiography performed 12 months or more after operation All but 1 of the patients had stones in the gallbladder and 18 (25%) had stones in the common duct Operative cholangiography was performed before removal of the gallbladder by injection of 35% Diodrast® down a fine catheter inserted into the common duct via the cystic duct In another group of 15 patients intravenous cholangiography was performed before operation and the diameter of the common duct was compared with that of the duct as shown on operative cholangiography The results obtained by the two methods in these ca es were similar thus indicating that preoperative drugs and anesthetics given to the patients who had operative cholangiography did not affect the validity of the comparison

(7) B M J 1 329 33 Feb 7 1959

Operative cholangiography revealed that 14 of 18 patients with a common duct diameter of 11 mm or more had stones in the duct whereas only 1 of 8 patients with a duct diameter of 10 mm had a stone in the duct Though it is apparent that there is a considerable range in diameter of the normal common duct it is suggested on the basis of these findings and the general shape of the distribution curve (Fig 87) that 10 mm represents the usual upper limits of normal No duct

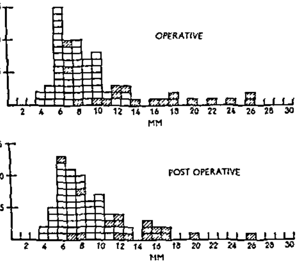


Fig 87 —Diag m how diamet f common b l d ct all 73 case meas- d ope t d post perat ch l g g am Ea h ecta gle p ese t l d h t h g d t that cal ul w fou d d ct rned (Court y f Le Q L P t l B t. M J 1 329 33 F b 7 1959)

should be regarded as definitely dilated unless its image measures 12 mm or more

The diameters of the common bile duct in the main series of 73 patients were similar at operation and postoperatively No instance was found of a duct of normal caliber on the operative cholangiogram increasing in diameter by 2 mm or more Although the duct diameter appeared smaller by 2 mm or more on postoperative cholangiography in 5 of 16 patients with a dilated duct on operative cholangiography (over 12 mm diameter) there was no clear tendency for a dilated duct to diminish in size after removal of calculi

No correlation was noted between continuation of symp

toms after cholecystectomy and size of the bile duct Of 15 patients with a bile duct of 12 mm diameter or more on post operative cholangiography 14 had no symptoms related to the biliary system Of 18 patients with symptoms possibly or probably due to some disorder of the biliary system 15 had a common duct measuring 10 mm or less The finding of a dilated bile duct on intravenous cholangiography performed after cholecystectomy is in itself of no significance in the absence of information about the size of the duct at the time of operation

► [*It is obviously difficult to define the diameter of the normal common bile duct An attempt to measure it directly at operation yielded figures ranging from 4 to 17 mm with an average of 8 85 mm (Ann. Surg 149 249 1959) The major point gained from the study here reported is that failure of a dilated bile duct to decrease in size after removal of gallstones does not necessarily indicate continuing obstruction of the duct —Ed.*]

Serum Desoxyribonuclease Activity and Pancreatic Damage were studied by J K Donahue J C Houck and R J Coffey[8] (Georgetown Univ) in dogs to assess the diagnostic significance of this enzyme determination and to compare it with serum amylase measurements

In 3 dogs the main pancreatic duct was sectioned so that it drained freely into the peritoneal cavity The serum level of desoxyribonuclease did not rise but significant elevation in serum amylase was found in each animal Gross pathologic examination showed some peritonitis but each pancreas was normal Rise in serum amylase was not manifestation of intrinsic pancreatic disease but merely reflected absorption of the enzyme across the peritoneum

When the main and accessory pancreatic ducts were ligated the pancreas became small and fibrotic and serum amylase rose markedly but desoxyribonuclease activity did not increase About 3 mg crystalline trypsin dissolved in 3 ml isotonic saline when injected into the parenchyma of the pancreas of 3 dogs produced an edematous organ and a normal serum amylase Serum desoxyribonuclease activity rose substantially reaching its peak on the 6th day Ethionine 100 mg/kg body weight injected intraperitoneally caused slight and transient elevation in serum desoxyribonuclease activity Serum amylase remain unaffected Pathologic findings in the pancreas were minimal

About 5 ml preprandial bile was aspirated from the gall bladder of each dog and injected into the lumen of the pre

(8) Surg 44 10 0 1078 December 1958

viously ligated main pancreatic duct Subsequently circulating concentrations of desoxyribonuclease and amylase activity rose markedly The pancreas showed parenchymal hemorrhage and necrosis In 3 other dogs a mixture of 4 ml preprandial bile and 1 ml trypsin solution was injected into the ligated main pancreatic duct Rise in the serum levels of desoxyribonuclease and amylase activity ensued the pancreas becoming hemorrhagic and necrotic

About 5 ml of 1 2 dilution of meningococcic toxin was injected into the ligated main pancreatic duct of dogs To produce a Shwartzman reaction a challenging dose of 5 ml of 1 10 dilution of this material was injected intravenously 24 hours later Serum desoxyribonuclease and amylase activities showed substantial elevations above normal The pancreas though grossly normal showed hemorrhage and inflammation microscopically

PATHOLOGIC FINDINGS AFTER PANCREATIC DAMAGE

			M AO		M	RC
F tul	P rit					
Ligat	F b		0	0	++	0
Tryps	M ttl g			+		++
Eth nin	H m l b			0		
Bil l g t	Hem h b d fil			++	++	++
B l l g t trvp	F b		++	++		++
Schw t m	N rm l			++		0

Obstruction of the pancreatic ductal system may be wholly responsible for elevations in serum amylase activity whereas elevations in serum desoxyribonuclease activity are associated solely with necrosis of pancreatic parenchyma

Leucine Aminopeptidase Activity Observations in Patients with Cancer of Pancreas and Other Diseases are presented by Alexander M Rutenberg Julius A Goldbarg and Esteban P Pineda[9] (Harvard Med School) Leucine aminopeptidase is a proteolytic enzyme that can hydrolyze l leucyl peptides It is found in bacteria plants and animals and has been demonstrated in all human tissues with high activity in the duodenum kidney and liver The intracellular function of this enzyme probably involves hydrolysis of a peptide bond near an l leucine residue or transfer of l leucine from one peptide molecule to another In the small intestine this peptidase is active in the terminal phases of protein digestion The authors demonstrated it regularly in gastric juice bile

(9) N w E gl d J M d 259 469 472 S pt 4 1958

and duodenal secretion in pleural peritoneal and cerebro spinal fluid and in the urine and serum

Leucine aminopeptidase activity in serum and urine was measured by a chromogenic substrate beta naphthylamine liberated by enzymatic hydrolysis was assayed colorimetrically Leucine aminopeptidase activity was assayed in the serums of 300 patients and the urines of 200 patients before treatment Diagnosis of cancer was established histologically

Mean serum activity and its standard deviation are 142 ± 29 units for men and 130 ± 27 units for women All determinations of activity in the serums and urines of 14 patients with cancer of the pancreas showed striking elevations Multiple blood transfusions or intravenous fluid infusions and electrolyte therapy did not alter serum or urine enzymatic activity There was no correlation between leucine aminopeptidase activity and intensity or duration of icterus Serum levels in patients with cancer of the head of the pancreas averaged 683 units After bypass operation serum activity decreased progressively immediately after operation

In 11 patients with lymphomas or leukemias urinary peptidase was markedly elevated Serum leucine aminopeptidase activity was 200 units or less in all patients It was normal preoperatively in 82 patients with cancer not involving the pancreas liver or hemopoietic system In 7 patients with nonpancreatic cancer and hepatic metastases serum values were 280-680 units Five with acute pancreatitis had moderate elevation in serum activity

The difference between the means of serum activity in patients with cancer of the head of the pancreas and those with common duct stone was highly significant In 23 (87%) of 26 patients with acute or chronic cholecystitis and cholelithiasis including 3 with gangrenous cholecystitis perforation and bile peritonitis serum leucine aminopeptidase activity was normal Patients with primary liver disease usually had significantly lower serum elevations than those with cancer of the head of the pancreas

Normal leucine aminopeptidase rules out cancer of the head of the pancreas High serum levels in patients with cancer imply a poor prognosis

► [Like so many other enzyme tests this test occasionally points brilliantly to the correct diagnosis but its specificity for pancreatic neoplasm is not substantiated by other workers In particular disorders leading to an obstructive type of jaundice may cause a false positive —Ed]

METABOLISM

PHILIP K. BONDY M.D.

PART VI
METABOLISM

THE ADRENAL GLAND

Loss of ACTH Activity Following Incubation of Pituitary Tissue Inhibition by Glucagon and by Pitressin® A M Barrett and George Sayers[1] (Western Reserve Univ) found that ACTH activity rapidly disappears from homogenates of anterior lobes of rat pituitary incubated at 37 C in plasma or water Activity disappears relatively slowly from intact anterior lobes incubated in plasma at 37 C Loss of ACTH activity is probably due to the action of a proteolytic enzyme or enzymes Destruction is markedly slowed at 5 and 100 C The optimum pH for the destructive system is about 9 0 Addition of glucagon or Pitressin® to the incubates inhibits destruction of ACTH

The glycogenolytic activity of glucagon is dramatically increased by adding it simultaneously with ACTH or insulin to liver slice Added polypeptides are presumed to act by substrate competition in decreasing the rate of destruction of glucagon by tissue proteolytic enzymes Glucagon and Pitressin® may be acting by a similar mechanism in protecting ACTH activity in incubated pituitary However the exact nature of the protective action competitive inhibition or noncompetitive inhibition remains to be established This would involve isolation and characterization of the enzyme(s) concerned with destruction of ACTH activity It would be of interest to establish whether ACTH glucagon and Pitressin® are substrates of the same enzyme system

Plasma proteins and casein in contrast to glucagon and Pitressin® exert no or a negligible inhibitory influence on the ACTH inactivity system which suggests that the inhibitory effect is confined to polypeptides Certain substances increase the quantity of ACTH in the medium of incubated pituitary This increase has been ascribed to release of

(1) Endocrinology 6 637 645 May 1958

ACTH from isolated pituitary and the in vitro system has been employed as an assay for the corticotropin releasing factor (CRF) However the acceptance of increase in ACTH in the medium as a measure of CRF activity should be cautious The added substance may act to inhibit destruction of ACTH increased quantities of activity in the medium may be at least in part a consequence of inhibition of destruction rather than of stimulation of release of ACTH

► [This paper suggests one of the problems arising in the search for the substance or substances responsible for controlling the release of ACTH from the pituitary Prior work by Saffran and co workers and by Guillemin and Hearn (1956 57 YEAR BOOK p 617) had suggested that a polypeptide somewhat comparable to vasopressin might be the active agent The difficulties of interpreting in vitro studies such as those previously quoted is apparent from the present paper —Ed]

Quantitative Determination of Urinary Cortisol Metabolites Tetrahydro F Allo Tetrahydro F and Tetrahydro E Effects of Adrenocorticotropin and Complex Trauma in the Human Norman I Gold Elaine Singleton David A Macfarlane and Francis D Moore[2] (Boston) evaluated several metabolites of cortisol in the urine of persons given adrenocorticotropin and cortisol Similar studies were made with patients having surgery or burns The compounds evaluated were tetrahydrocortisol (3α 11β 17α 21 trihydroxy pregnan 20 one) allo tetrahydrocortisol (3α 11β 17α 21 tetrahydroxyallopregnan 20 one) tetrahydrocortisone (3α 17α 21 trihydroxypregnan 11 20-dione) and cortisol (11β 17α 21 trihydroxy Δ^4pregnane 3 20 dione)

Increase was noted in both rate of excretion of each metabolite—tetrahydrocortisol allo tetrahydrocortisol and tetrahydrocortisone—and ratio of urinary tetrahydrocortisol to tetrahydrocortisone (1) during and after surgery (2) after intravenous administration of 25 I U of adrenocorticotropin to normal persons (3) after administration of 50 mg cortisol intravenously to 1 normal person and (4) in 4 patients with severe burns (Fig 88) In 3 patients with fatal burns the tetrahydrocortisol tetrahydrocortisone ratio rose to extremely high values before death suggesting factors which limit conversion of cortisol to tetrahydrocortisone i e inhibition of oxidation at the 11 position There was no indication that formation of allo tetrahydrocortisol was grossly impaired

The tetrahydrocortisol tetrahydrocortisone ratio was ele

( ) J Cl In t 37 813 8 3 J 1958

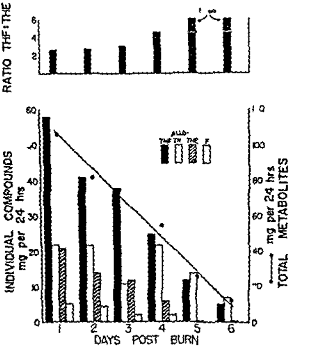


Fig 88—Urinary cortisol metabolites in a severely burned man aged 47 who died on day 7 (Courtesy of Gold N I *et al* J Clin Invest. 3 813 8 3 Jun 1958)

vated for a month in a chronically ill patient with ulcerative colitis pulmonary embolism and empyema who had had major abdominal surgery Allo tetrahydrocortisol was not detected during this period After 5 months convalescence urinary pattern was normal allo tetrahydrocortisol was present

Trauma in man can give rise to variations in over all metabolism of cortisol

► [Much of the information pertaining to the activity of the adrenal cortex in human beings is derived from studies of the amounts of corticosteroid breakdown products in the urine The implicit assumption in such studies is that the amount of urinary steroid is directly related to the amount of steroid secreted by the adrenal cortex and this assumption supposes in turn that the metabolic pathway of the hormone are relatively constant. Gold's paper shows that this basic set of assumptions is not entirely correct It implies that the interpretation of studies of urinary *steroid excretion* may need to be re-evaluated This problem is considered in relation to the 17 keto teroids in the next paper and in regard to allos

ACTH from isolated pituitary and the in vitro system has been employed as an assay for the corticotropin releasing factor (CRF) However the acceptance of increase in ACTH in the medium is a measure of CRF activity should be cautious The added substance may act to inhibit destruction of ACTH increased quantities of activity in the medium may be at least in part a consequence of inhibition of destruction rather than of stimulation of release of ACTH

► [This paper suggests one of the problems arising in the search for the substance or substances responsible for controlling the release of ACTH from the pituitary Prior work by Saffran and co-workers and by Guillemin and Hearn (1956-57 YEAR BOOK p 617) had suggested that a polypeptide somewhat comparable to vasopressin might be the active agent. The difficulties of interpreting in vitro studies such as those previously quoted is apparent from the present paper —Ed]

Quantitative Determination of Urinary Cortisol Metabolites Tetrahydro F Allo-Tetrahydro F and Tetrahydro E Effects of Adrenocorticotropin and Complex Trauma in the Human Norman I Gold Elaine Singleton David A Macfarlane and Francis D Moore[2] (Boston) evaluated several metabolites of cortisol in the urine of persons given adrenocorticotropin and cortisol Similar studies were made with patients having surgery or burns The compounds evaluated were tetrahydrocortisol (3α 11β 17α 21 trihydroxy pregnan 20 one) allo tetrahydrocortisol (3α 11β 17α 21 tetrahydroxyallopregnan 20-one) tetrahydrocortisone (3α 17α 21 trihydroxypregnan 11 20-dione) and cortisol (11β 17α 21 trihydroxy Δ^4pregnane 3 20 dione)

Increase was noted in both rate of excretion of each metabolite—tetrahydrocortisol allo tetrahydrocortisol and tetrahydrocortisone—and ratio of urinary tetrahydrocortisol to tetrahydrocortisone (1) during and after surgery (2) after intravenous administration of 25 I U of adrenocorticotropin to normal persons (3) after administration of 50 mg cortisol intravenously to 1 normal person and (4) in 4 patients with severe burns (Fig 88) In 3 patients with fatal burns the tetrahydrocortisol tetrahydrocortisone ratio rose to extremely high values before death suggesting factors which limit conversion of cortisol to tetrahydrocortisone i e inhibition of oxidation at the 11 position There was no indication that formation of allo tetrahydrocortisol was grossly impaired

The tetrahydrocortisol tetrahydrocortisone ratio was ele

(2) J Clin I st. 37 813 823 J 1958

olism Studied with Albumin I^{131} Studies of serum albumin turnover with albumin I^{131} as a tracer have revealed a narrow range of values averaging about 200 mg/kg/day in normal men and in patients with congestive heart failure In other disease states abnormalities in the rate of synthesis and/or degradation have been observed In most patients with marked proteinuria the amount of albumin undergoing metabolic degradation has been diminished significantly whereas the rate of synthesis has remained at normal levels In contra t the abnormally high rate of albumin catabolism in thyrotoxicosis has been observed to be compensated by an augmented synthesis of albumin The major effect of the adrenocortical hormones on protein metabolism has been interpreted as an increased rate of catabolism a decreased rate of synthesis or a combination of both effects

M A Rothschild S S Schreiber M Oratz and H L McGee[4] (New York) studied the distribution and metabolism of albumin using species specific albumin I^{131} in 8 female rabbits and 5 male patients before and during administration of adrenocortical hormones Under the influence of cortisone albumin degradation increased by 58% in the animals and augmented albumin synthesis compensated for 91% of this increased albumin destruction In human beings albumin degradation increased 27% and increase in synthesis replaced 48% of the albumin degraded in excess of the control values

Serum albumin metabolism is significantly altered during administration of certain adrenocortical hormones Moderate to marked increase in rate of albumin catabolism is associated with increase of similar magnitude in rate of albumin synthesis so only negligible loss of body albumin stores results These observations clearly provide no support for the thesis that these hormones exert an antianabolic effect on all protein metabolism The small defect in albumin balance was derived mainly from the extravascular stores a finding also recorded after administration of large doses of desiccated thyroid

► [It appears that the negative nitrogen balance associated with the administration of adrenocorticoids may be partially or completely reversible at least as far as plasma albumin synthesis is concerned f sufficient raw material are available to permit the accelerated synthesis noted in this study —Ed]

(4) J Cl I t 37 12 9 1 35 S pt mb 1958

terone in the paper by Ulick in the section on Electrolytes p 615—Ed]

Differences in Metabolism of Reichstein s Substance S in Normal Adults and Children are reported by Alfred M Bongiovanni Walter R Eberlein and Joan L Caddell[3] (Philadelphia) with the technical assistance of Willfried Eder Excretion of corticoids in the urine of human beings remains relatively constant throughout life when referred to body surface area but excretion of 17 ketosteroids in the urine progressively rises during adolescence In the adolescent male increased 17 ketosteroid excretion is in part attributable to developing testicular function It is believed that in both sexes increased adrenocortical secretion at puberty is also responsible though the exact nature of the alteration that occurs is unknown Other workers have suggested that a second adrenocorticotropic hormone specifically responsible for stimulation of 17 ketosteroid production appears during this era of life in human beings

The increased puberal excretion of 17 ketosteroids derived from the adrenal cortex may also reflect altered extra adrenal metabolism of steroids Certain of the C 21 adrenocortical steroids are known to be degraded to 17 ketosteroids in the body The greater quantities of urinary 17 ketosteroids appearing with attainment of maturity might then arise from increased conversion of C 21 steroids to such metabolites In order to test this hypothesis Δ^4 pregnene 17α 21 diol 3 20 dione (substance S) was given by various routes to children and adults and excretion of 17 ketosteroids and other metabolites was measured

Mature subjects showed a greater conversion of substance S to 17 ketosteroids That the increment was primarily due to a rise in urinary excretion of etiocholanolone suggests another mechanism for the rise in urinary excretion of 17 ketosteroids at adolescence apart from direct genesis of gonadal or adrenal C 19 steroids *per se* In addition adults produced greater quantities of urinary metabolites reduced at C 20 It also appears that substance S is more readily reduced at C 20 than hydrocortisone Tetrahydro S was isolated and identified in the urine after administration of substance S another compound was isolated and tentatively identified as pregnane 3α 17α 20ξ 21 tetrol

Effects of Adrenocortical Hormones on Albumin Metab

(3) J Cl I t 37 1087 109 Augu t 1958

dent in each The adrenal cortex is probably involved in the clinical manifestations of this disorder

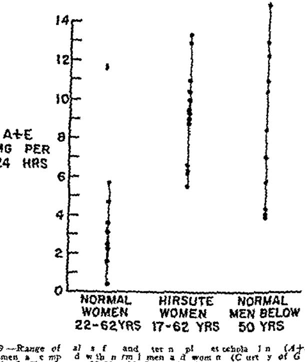
The principal alteration was elevated production of androsterone and etiocholanolone In each of the hirsute women abnormally large amounts of these two substances were produced as compared with normal women of commensurate age the amounts equaled production of these steroids in young normal men (Fi 89) This is especially significant because besides the sex differences in adrenal function the male gonad contributes a portion of these metabolites

The evidence is substantial that in women as well as in men the adrenal cortex elaborates the principal precursors of the urinary metabolites studied In castrated men and women with intact adrenals androsterone and etiocholanolone production continues but not if the adrenal is also removed Production of these hormones in both sexes is markedly increased after stimulation with corticotropin and decreased after suppressive doses of cortisone These findings are explicable only if the adrenal cortex produces the precursors to these substances In hirsute women cortisone or hydrocortisone administration results in fall in androsterone and etiocholanolone production to levels observed in normal nonhirsute women

Elevated levels of androsterone and etiocholanolone in hirsute women reflect adrenocortical hyperfunction Apparently the steroid metabolites isolated in abnormal amount are the same as those that result from metabolic transformation of known androgens The principal features in these women are unmistakably androgenic Thus clinical evidence and the chemical structure of the metabolites are compatible with the interpretation that the adrenocortical secretion in these subjects is characterized by excessive production of adrenal androgen Some of the women showed elevated production of C_{19} 11 oxygenated steroids Thus increased adrenal function was not limited to metabolites of 11 desoxy steroid hormones but these showed greatest elevation

The demonstrated adrenocortical hyperactivity in the 4 women with Stein Leventhal syndrome was particularly interesting Previous studies of neutral 17 ketosteroids had been nonrevealing More detailed steroid analyses would probably reveal significant hormone alterations in a num

Adrenocortical Hyperfunction in Idiopathic Hirsutism and Stein Leventhal Syndrome T F Gallagher Attallah Kappas Leon Hellman M B Lipsett O H Pearson and C D West[5] (Sloan Kettering Inst) studied 13 women unselected except for presence of obviously excessive hair growth Specific quantitative alteration in steroid produc



F g 89—Range of al s f and ter n pl et chola 1 n (A+E) f h r te women a c mp d w th n rm l men a d wom n (C urt y of G llagh T F et al J Cl n In est 37 794 99 J 1958)

tion distinguished these patients from normal women Adrenal steroid hormones were elaborated in excess largely adrenal androgen Four women with hirsutism later proved to have Stein Leventhal syndrome were included because the sole criterion for inclusion was hirsutism Diagnosis was unequivocally established by direct examination of the ovaries These patients would have been classified as having hirsutism of undetermined cause if they had not later been subjected to laparotomy Adrenocortical hyperfunction was evi

(5) J Cl I e t 37 794 299 J e 1958

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ber of these women In fact altered adrenal function may be a significant or even primary influence in this disorder

Hirsute women in this study showed increased production of androsterone and etiocholanolone unaccompanied by increased secretion of hydrocortisone or chemically related hormones These women did not show signs and symptoms of Cushing s syndrome The biochemical lesion is an adrenal hyperfunction largely limited to the adrenal androgen

► [The *data* in this study are most important but the *interpretations* will not meet with uniform acceptance The assumption that the androgen responsible for hirsutism is secreted by the adrenal derives from the reduction in urinary 17 ketosteroid output and the change of steroid pattern after adrenal suppression with exogenous steroids However if the adrenal were putting out a normal amount of steroids and the androgen were coming from some other source the suppression of adrenal activity wo 'd still reduce the total amount of steroid in the urine The assumption that all 11 oxygenated 17 ketosteroids are derived from the adrenal may be correct in normal individuals but the recent demonstration by Savard Engel and others of the production of 11 oxygenated steroids by testicular tumors suggests that this specificity cannot be assumed to persist in all pathologic states —Ed]

Clinical Management of Idiopathic Hirsutism (Adrenal Virilism) William H Perloff Bertram J Channick Benedict Suplick and Elsie R Carrington[6] (Temple Univ) studied 45 women endocrinologically with particular emphasis on urinary excretion of 17 ketosteroid components In 7 patients hirsutism was part of a surgically verified Stein Leventhal syndrome in 22 it was associated with irregularities of menstruation and in 16 in whom it was generally less severe than in the others hirsutism coexisted with regular menstrual rhythm The level of the $C_{19}O$ fraction including strongly androgenic substances was uniformly elevated whereas that of the $C_{19}O_3$ fraction containing weakly androgenic hormones was not

Prednisone in daily doses of 7 5 15 mg reduced total neutral 17 ketosteroid excretion to normal in all patients and gave fair to good improvement of hirsutism Amenorrhea oligomenorrhea and menometrorrhagia responded remarkably to prednisone Clinical results were gratifying Physiologically they strengthen the belief that in hirsutism of this type ovarian changes are secondary to primary changes in the adrenals

Exploration is not always necessary to establish diagnosis of the Stein Leventhal syndrome it may be assumed in

(6) J A M A 167 2041 2047 Aug 23 1958

voung women with amenorrhea oligomenorrhea or meno metrorrhagia hirsutism and enlarged ovaries in whom other causes of hirsutism have been eliminated The level of uri nary neutral 17 ketosteroids may be within normal range but of 17 patients with a proved or presumed Stein Leventhal syndrome 16 showed levels of the $C_{19}O_2$ fraction above 6 mg Obesity uterine hypoplasia and/or underdeveloped breasts may also coexist Ovarian enlargement may not be detectable on pelvic examination and other diagnostic tech nics such as culdoscopy and/or pneumoperitoneum and x ray may be required Medical therapy should be attempted before wedge resection is performed

Once the diagnosis is established treatment should be initiated early to prevent or delay permanent ovarian dam age Prednisone the drug of choice should be given in re quired doses for at least 6-12 months If menstrual status im proves therapy should be continued for a longer but as yet undetermined period The daily dose of hormone is governed by clinical results and urinary 17 ketosteroid levels deter mined monthly It is begun with 10 mg /day and adjusted by increments of 2 5 mg The level of total neutral 17 keto steroids should be maintained between 6 and 10 mg and that of the $C_{19}O_2$ fraction should be suppressed be low 5 mg Prednisone metabolites affect 17 ketosteroid lev els insignificantly

► [Studies such as those of Callagher and co-workers cited in the article preceding th s one have led to a widespread use of suppressing doses of nonandrogenic adrenal corticoids in the treatment of id opathic hirsutism This type of treatment is effective only when adre ial cortical hyperactivity is truly the cause of hirsutism It has been our experience (in contrast to that of Perloff) that patients with the Stein Leventhal syndrome do *not* respond to cort coids and certa nly patients with famil al hirsutism are unaffected by this treatment. For th s reason it is essential that suppres sant therapy be undertaken only after thorough evaluation of the function of the adrenal glands Studie at lea t as elaborate as those performed by Perloff should be required before an attempt at adrenal suppression is undertaken It is most important to avoid therapeutic trials without proper prel minary studies

An important paper concerned with the pattern of adrenal cort coid ex cretion in patients with more typical androgenital disease has been pub l shed by Bergstrand B rke and Plantin (Acta endocrinol 30 500 1958) These authors point out that in certain cases the usual explanation for the and ogen tal syndrome (see 1954 55 YEAR BOOK pp 612-615 and 1956 57 p 631) may not fit the pattern of steroids found in the urine —Ed]

Diagnosis and Treatment of Cushing s Syndrome are dis cussed by A Labhart E R Froe ch and W Ziegler[7] (Med

(7) S hw med W h sch 89 44 53 J 10 1959

Univ Clinic Zurich) The syndrome is due to overproduction of adrenocortical hormones especially the glucocorticoids Overproduction may be due to malignant or benign adrenocortical tumors or to bilateral hyperplasia In observations on 9 women and 1 man 2 adrenals were studied at autopsy and 7 after adrenalectomy Of the latter 1 showed adenoma and the others were hyperplastic weighing between 11 and 27 5 Gm Among the patients studied at autopsy the pituitary showed a chromophobe basophil adenoma in 1 and minimal basophilia besides cancer metastases in another The commonest clinical symptom present in all patients was moonface followed in frequency by latent diabetes in 8 patients and back pain due to osteoporosis in 7 Overweight and amenorrhea were less common thus their absence does not speak against Cushing s syndrome

It may be difficult to diagnose Cushing s syndrome in the beginning when only a few symptoms are present Various laboratory tests however may facilitate the diagnosis The eosinophil count repeated several times may be a valuable screening test counts above 100/cu mm make the presence of Cushing s syndrome improbable This test failed in only 1 out of 10 patients Whereas the amount of the 17 ketosteroids in the 24 hour urine is normal or only slightly elevated the 17 hydroxycorticoids are usually increased However because of the day by day fluctuations in 17 hydroxycorticoid excretion single normal values do not exclude the diagnosis In a borderline case the ACTH tests may help out and will at the same time assist in differentiating a tumor from hyperplasia It has been shown that the pathologic changes in the adrenal cortex determine the response of the latter to ACTH stimulation

In Cushing s syndrome the treatment of choice is surgical If there is absolute contraindication to surgery testosterone therapy may be tried The anabolic testosterone is antagonistic to the catabolic activity of cortisol and may produce some palliation Irradiation of the pituitary gland may occasionally be effective but the recurrence rate is high Hypophysectomy is indicated in the rare instances in which the syndrome is due to a space occupying pituitary tumor

It is the consensus that bilateral total adrenalectomy is the surgical treatment of choice Subtotal resection precludes substitution therapy if the remaining adrenal t s do not

atrophy However latent Addison di ease develops in this situation and an addisonian crisis can be expected when any stress occurs Even more important is the possibility of an incomplete remission and especially of a recurrence after subtotal adrenalectomy

Cushing s Syndrome—*Diagnosis*—According to R I S Bayliss [8] increased secretion of adrenocortical hormones is the cause of Cushing s syndrome In some instances in creased secretion of glucocorticoids is accompanied by en hanced production of androgenic steroids and the clinical features of hyperadrenalism may range from classic Cush ing's syndrome at one end of the scale to virilization at the other with intermediate forms between If retained at all the term Cushing s syndrome should be reserved for patients with the clinical features of excess glucocorticoid secretion but wherever possible especially in mixed cases the disor der should be classified in terms of the particular steroids secreted in excess

Among 19 patients with Cushing s syndrome confirmed by clinical and hormonal assessment the commonest symptoms were moon facies facial hirsutism hypertension and alteration in skin texture whereby the skin loses elas ticity and can be picked up in the fingers with an absence of the normal underlying fat Development of purple striae seems to depend on the combination of this skin atrophy with truncal obesity X ray evidence of osteoporosis was found in 11 patients

The plasma 17 hydrocorticosteroid levels were in most instances above the upper limit of normal 18 µg /100 ml but often not strikingly so In 5 patients the level was within the normal range but the infusion of ACTH caused a greater adrenal response than occurs in normal persons The urinary excretion of 17 ketosteroids was raised in some patients but abnormal values were not found as often as increased plasma 17 hydroxycorticosteroid levels Although high 17 keto steroid values may confirm the existence of adrenal disease normal values in no way exclude Cu hing s syndrome

The distinction between adrenal hyperplasia adenoma or carcinoma may be made by palpating an adrenal tumor which usually indicates a carcinoma is present by finding enlargement of the sella turcica which suggests a pituitary

(8) P oc R y S M d 50 761 764 O t be 1957

adenoma and adrenal hyperplasia or by presacral air insuffla tion Often hormone assays make the differentiation Ex cretion of 17 ketosteroids is usually high in adrenal carci noma low in adenomas and intermediate in hyperplasia but the overlap among the three is so great that reliance can *not be placed on this differentiation in individual patients*

Treatment by adrenalectomy —A Stuart Mason[9] presents data on 11 males and 41 females aged 14 62 with Cushing s syndrome in the absence of an adrenal tumor who under went adrenalectomy and were followed a minimum of 9 months Total mortality rate was 25% but for patients who survived 3 months after operation the rate was 9 3% during the observation period Results of adrenalectomy were excel lent in terms of recovery from Cushing s syndrome Only 2 survivors showed persistent but nonprogressive adrenal hy perfunction and both refused further treatment

Some operations were performed in two stages it is ad *visable to perform the full operation in one stage* whenever the patient s condition permits Total removal of one of the adrenals with subtotal resection of the other is preferable to subtotal resection of both One patient had a relapse some time after resection of both adrenals and it was impossible *to know which adrenal to approach for further surgery* Re moval of 50% or less of adrenal tissue failed to control Cush ing s syndrome except in 2 patients over age 45 who also had postoperative deep x ray therapy to the pituitary Re moval of 90 95% of adrenal tissue gave the best results *in terms of curing Cushing s syndrome but many patients* were left with permanent adrenal hypofunction In 6 pa tients the original disease was cured by removal of 75% or more of adrenal tissue but relapse subsequently occurred

The margin between removing enough adrenal tissue to prevent relapse and the amount that causes adrenal hypo function is very narrow with virtually no margin in patients under 25 years of age Consequently total adrenalectomy is advisable in this group because of rather than despite their age Patients over 45 are more likely to die after opera tion than are younger patients *particularly after total adre* nalectomy Older patients are also likely to show irreversible damage to the vascular system Earlier diagnosis is impor tant but failing this subtotal adrenalectomy with removal

(9) Proc Roy S M d 50 766 770 Oct be 1957

of 75% of the tissue or even unilateral total adrenalectomy is preferable to more radical operation Deep x ray therapy to the pituitary should be given postoperatively Patients aged 25-45 should be treated by subtotal adrenalectomy with removal of 85 90% of adrenal tissue

In the discussion A W Spence stated that normal adrenal glands are occasionally found in Cushing s syndrome indicating that the histologic appearance of an endocrine gland is not necessarily an index of the amount of hormone it is secreting He added that in patients with Cushing s syndrome due to adrenocortical hyperplasia treatment depends on severity of the disease In incomplete or milder cases removal of 1 gland might be satisfactory although admittedly relapse sometimes occurs The effect of irradiation of the pituitary gland has on the whole been disappointing although in 1 patient with the complete syndrome removal of 1 gland—followed some months later by irradiation of the pituitary —produced a satisfactory response In severer cases choice of treatment rests between subtotal and total adrenalectomy Since the advent of cortisone total adrenalectomy is preferred

A C Crooke and his colleagues stated that they were disappointed with subtotal adrenalectomy for Cushing s syndrome because it was difficult to determine how much gland to remove and because recurrence of initial symptoms or development of adrenocortical insufficiency was common They had therefore performed total adrenalectomy recently but were anxious about what complications might arise from this procedure In 4 patients with total adrenalectomy for Cushing s syndrome or for malignant hypertension who were treated with 37 5 50 mg cortisone daily pain in the spine with persistent slight hypercalcemia developed Crooke and his co worker suspected that the bone pains and hypercalcemia were associated with progressive lo s of calcium and osteoporosis as a result of a specific adrenocortical deficiency

O Garrod and his co workers stated that they had studied steroid excretions in 2 patients with Cushing s syndrome due to proved adrenal carcinoma Both patients had severe hypokalemia (plasma potassium levels of 2 7 mEq /L and a low level of total exchangeable body potassium 22 3 and 24 3 mEq /kg respectively (normal range 35 48 mEq /kg)

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(9) Proc Roy Soc Med 50 766-770 Oct 1957

cism a chromophobe tumor of the pituitary gland was found which was secreting large quantities of ACTH

Woman 33 presented with typical Cushing syndrome At bilateral adrenalectomy the left adrenal weighed 7 Gm and the right 6 5 Gm Hyperplasia primarily of the zona fasciculata was present in both The patient was maintained on 0 1 mg 9α fluorohydrocortisone 37 5 mg cortisone and 1 2 Gm potassium chloride daily

Within 2 years menorrhagia and increasing skin pigmentation developed Amenorrhea recurred 6 months later Three years after surgery vision in the left eye had decreased and intense buccal pigmentation appeared Perimetry showed complete loss of the temporal field on the left and almost complete loss on the right The nasal fields were moderately restricted The sella turcica was enlarged

No thyroid stimulating hormone activity was detectable in the plasma (normal) and urinary follicle stimulating hormone excretion was below normal range Urinary output of melanocyte stimulating hormone and the plasma ACTH level were markedly elevated

Deep x ray therapy to the pituitary gland was started but because of sudden hemorrhage surgery was done A hemorrhagic partially liquefied tumor which histologically resembled a chromophobe adenoma was removed

Recovery was uneventful the cutaneous pigmentation decreased slightly and the visual fields returned to normal A second course of deep x ray therapy was given approximately 1 900 r in 26 days The patient was then discharged on cortisone (12 5 mg twice daily) 9α fluorohydrocortisone (0 1 mg daily) potassium chloride (1 Gm 3 times a day) and 90 mg thyroid daily

Immediately after operation plasma ACTH was not detectable but in the next 4 months it was found in amounts similar to those in other patients with hypoadrenocorticism Unfortunately the plasma ACTH had not been determined before adrenalectomy

The tumor had apparently been secreting melanocyte stimulating hormone as well as ACTH The decrease in pigmentation after its removal was impressive This case suggests the possibility that adrenalectomy acted to stimulate ACTH secretion and the production of a pituitary adenoma

► [A similar case is reported by Rees and Bayliss (Proc Roy Soc Med 52 256 1959) Although at present this seems to be a rare complication of the surgical treatment of Cushing syndrome it may prove to be more common on further follow up In any event careful observation of the status of the pituitary appears desirable during the postoperative period in patients in whom functioning adrenal cortical hyperplasia has been treated by bilateral total adrenalectomy

An additional case of Cushing s syndrome caused by an ovarian tumor is reported in the section on the Ovary —Ed]

Growth Suppression in Asthmatic Children Receiving Prolonged Therapy with Prednisone and Methylprednisolone Thomas E Van Metre Jr and Herman L Pinkerton[2]

(2) J Allergy 3 103 113 M Ap 1959

The daily urinary steroid excretions in the first patient were aldosterone 4 μg cortisol 1 200 μg In the second patient before removal of the adrenal tumor they were aldosterone 5 8 μg cortisol 370 μg corticosterone 34 μg after removal of the tumor the plasma potassium level having risen to 4 mEq /L and the exchangeable body potassium level to 35 6 mEq /kg steroid excretions were aldosterone 15 μg corticol 5 3 μg corticosterone 4 μg Normal ranges of steroid excretion were aldosterone 5 22 μg cortisol 13 86 μg corticosterone 2 2 9 μg It would seem therefore that the severe electrolyte disturbances in these patients were due not to excessive aldosterone secretion the output of this mineralocorticoid hormone being at the lower limit of normal but to excessive secretion of one or both of the so called gluco corticoids—cortisol and corticosterone—both of which might have powerful mineralocorticoid actions in large doses comparable with the amounts sometimes secreted in Cushing s syndrome

► [The problems of diagnosis and treatment of Cushing s syndrome are still troublesome In previous years data concerning the clinical and laboratory picture of this disease have been presented in the YEAR BOOK (1954-55 p 617 and 1958 59 p 649) Further important information has been contributed by Jailer and co workers (J Clin Invest 38 357 1958) Na barro (J Clin Endocrinol 18 586 1958) and Laroche (Ann endocrinol 19 1074 1958) Although there are a few dissenting voices most observers seem to agree that there is no clinical or laboratory method which distinguishes in a satisfactory manner between hyperplasia and tumor as a cause of hyperadrenocorticism Our practice has therefore been to explore the adrenals of patients with Cushing s syndrome and to do bilateral total adrenalectomy in all cases except when unilateral tumor is associated with contralateral atrophy In this respect we agree with Crooke and disagree with Mason cited above Dissenting opinions have been quoted previously in the YEAR BOOK (e g Bishop *et al* 1955 56 p 616 and Dohan *et al* 1957 58 p 629 who feel that *irradiation of the pituitary plays an* important part in the treatment of these patients and Cope and Raker 1956 57 p 638 who *recommend subtotal adrenalectomy*) —Ed]

ACTH Producing Tumor of Pituitary Gland The association of adrenal hyperplasia with basophil tumors of the pituitary gland was first suggested by Cushing This type of tumor has since been thought to be at least one cause of Cushing s syndrome but elevated levels of ACTH have not been demonstrated in the plasma of patients with this syndrome Don H Nelson J W Meakin James B Dealy Jr Donald D Matson Kendall Emerson Jr and George W Thorn[1] (Harvard Med School) report a case in which 3 years after bilateral adrenalectomy for hyperadrenocorti

(1) N w E gla d J Med 259 161 164 J ly 24 1958

be logically attributed to steroid therapy It appeared first with onset of therapy the degree was roughly propor tional to the dose and when therapy was stopped growth rate became accelerated

Children receiving prolonged steroid therapy should be followed carefully The dose should be reduced below growth suppressing levels sufficiently often to permit re covery of any growth lost This must be done before the age when further skeletal growth is precluded by closure of skeletal epiphyses

Reversible Amyotrophy Complicating Treatment with Fludrocortisone is described by Kenneth MacLean and Pe ter H Schurr[3] (Guy s Hosp London)

Woman 49 underwent surgery for a craniopharyngioma Severe hypotension necessitated administration of 0 5 mg fludrocortisone daily for about a year During this period steroid diabetes and pro gressive muscular paralysis especially involving the legs developed The legs became completely paralyzed apart from a flicker of move ment at the ankles Within 3 days after discontinuation of fludrocor tisone movement of the legs began to return and this has increased steadily so that the patient could walk without support

In searching for a cause to explain the muscular weak ness various factors were considered Myopathy can follow excessive potassium loss and in view of the long continued administration of a strong mineralocorticoid this seemed to provide a possible explanation The serum potassium and ECG were both normal however which appeared to ex clude this hypothesis Thyrotoxic myopathy also seemed to be ruled out by the normal basal metabolic rate and by the absence of clinical evidence of thyrotoxicosis The possibil ity that the amyotrophy might be the result of the steroid diabetes was considered Diabetic amyotrophy has been de scribed by Garland and may occur early in the disease In Garland s patients the electromyograph gave varying re sults but in some as in the authors patient the lesion ap peared to lie in the region of the anterior horn cells Fur thermore the paralysis was reversible and improvement did not always begin immediately when the blood sugar was controlled In the authors patient rapid deterioration con tinued during the 1st month in hospital despite considerable

(3) L . 1 701 703 Ap 4 1959

(Johns Hopkins Univ) observed the growth of 13 children with intractable perennial asthma who had received prednisone prednisolone or methylprednisolone for 6 months or longer and compared the results to the growth of 52 children with perennial bronchial asthma who received no corticosteroid therapy

Before corticosteroid therapy was started linear growth was essentially normal During therapy growth was re

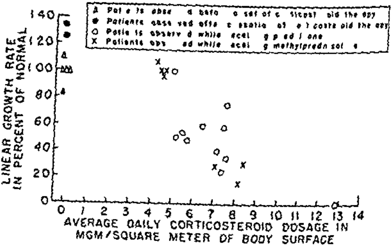


Fig 90 —R at n h p b twe n e age da ly c tico t d d g and l g wth r t s 13 pat t Ea h plott d p t n s t d t d r v d f m t last 6 o ec t e m ths f b e t n (Court y of) n M t T E J a d Pinker t H L J J All gy 3 103 113 M Ap 1959)

tarded when the average dosage for a 6-month or longer period exceeded 5 mg /sq m of body surface/day When the average dose was less growth was normal The degree of retardation was roughly proportional to dosage and appeared similar with either prednisone or methylprednisolone (Fig 90) After therapy was stopped linear growth rate was accelerated

Before therapy weight gain was more often subnormal than normal During therapy weight gain was normal or accelerated even when linear growth was retarded and the children appeared well nourished even obese At least 5 developed moon facies

The linear growth retardation observed in asthmatic children receiving prednisone and methylprednisolone can

daily requirements are low for needs of new tissue per se Widdowson and associates found about 2 200 mg sodium/ kg of fat free body weight irrespective of age or a final total body content of about 130 000 mg for a 70 kg man With a birth weight of 3 kg and cessation of growth at 16 average daily sodium requirement by the new tissues would be under 25 mg Of course requirements for growth are in addition to the minimal requirements That these estimates are of the proper order of magnitude is suggested by the balance studies made by Macy on growing children who were on a relatively high salt intake in which a total mean daily sodium retention of 246±280 mg was found

Among 1 346 adults classified according to salt intake at table 135 were classed as having a low 630 an average and 581 a high intake The 105 persons classified as having hypertension were distributed in nonrandom fashion as follows 61 among the persons with high 43 among those with average and only 1 among those with low salt intake The probability that the hypertensive patients would be distributed among the three groups in such a fashion by chance alone was calculated to be less than 1 in 1 000 The group with a low salt intake had significantly less ($P<0.01$) and the group with high intake significantly more ($P<0.02$) hypertension than would have been expected from random distribution Additional classification of these persons according to weight indicated that obesity further increased probability of hypertension

A salt appetite exists both in animals and man In animals the herbivores travel great lengths to reach salt licks the carnivores do not The sodium content of the diet of herbivores differs from that of carnivores in having a high potassium sodium ratio approximating 20 1 A carnivorous diet has only about 5 times as much potassium as sodium The human being who consumes an average of 10 Gm salt daily ordinarily will have a potassium sodium ratio of about 1 1 1 4

What these variations in relative potassium sodium intake mean in terms of physiologic processes is not clear Since there is no question that salt appetites can be induced in a variety of mammals is there evidence that these appetite are inborn? Dahl found *no evidence* of salt craving among persons on drastically reduced intakes Many per

improvement in the glycosuria and so other possible etiologic factors had to be considered

It has been reported that triamcinolone caused excessive loss of muscle tissue giving rise to the clinical appearance of a myopathy As triamcinolone (9α fluoro 16 hydroxy prednisolone) resembles fludrocortisone in possessing a fluorine atom in the 9α position in the steroid nucleus it was felt that fludrocortisone might be responsible for the muscular paralysis in this patient Her rapid improvement after discontinuation of fludrocortisone provides strong evidence that this steroid was playing a major part in producing the amyotrophy

► [New adrenal corticoids are being released by the pharmaceutical companies more rapidly than they can be evaluated by the clinicians For example the most complete studies published to date on prednisone and prednisolone have only just appeared (Pechet J Clin Invest 38 681 1959) A preliminary report on dexamethasone appeared in Lancet 1 1/3 Jan 24 1959—Ed]

ELECTROLYTES AND WATER

► Because the metabolism of salt and water is closely associated with the activity of the posterior pituitary gland and the action of aldosterone these hormones will be considered in the electrolyte section I am deeply grateful to my colleague Dr Franklin H Epstein who helped me select the papers in this section

Excellent reviews of the present state of our knowledge of aldosterone secretion have been published by August Nelson and Thorn (New England J Med 259 917 and 967 1958 and by Luetscher and Lieberman A M A Arch Int Med 102 314 1958) The effect of human growth hormone in increasing urinary aldosterone excretion is described in the section The Pituitary Gland—Ed

Salt Intake and Salt Need were studied by Lewis K Dahl[4] (Upton N Y) Approximate normal obligatory (or irreducible) daily sodium losses are as follows urine 5 35 mg stool 10 125 mg skin (nonsweating) 25 mg and total 40 185 mg The nonobligatory requirements would be chiefly due to sweat since estimates of loss from other bodily secretions and excretions suggest that these would not exceed an average of 10 15 mg a day No consideration is given here to need for additional amounts of sodium when new tissue is being laid down

Simple calculations indicate that even during growth

(4) N w E gla d J Med 258 115 1157 Jun 5 1 05 1 195

although not all hypertensive animals were hypercholesterolemic

At autopsy the organ weights were consistent for heart and kidney less so for adrenals Heart and kidney weight increased as the level of dietary sodium chloride increased Adrenal weight increased at high levels of high salt feeding but under this level only a slight trend without statistical significance was noted The basic finding on microscopic examination was a disorder primarily affecting the arterioles and small arteries seen most strikingly in the kidney and parenchymatous organs The glomeruli were enlarged but almost bloodless from swelling and vacuolation of endothelium and epithelium with large amounts of sudanophilic lipid The tubules were dilated and the epithelium was hyperplastic and swollen with lipid and hyaline droplets The small arteries and arterioles showed fatty degeneration of muscle cells and often smudgy eosinophilic necrosis Similar arteriolar lesions were found in other viscera especially the pancreas and testes

The median duration of life of rats eating 8 4% sodium chloride added to the basic ration (0 66% in potassium chloride potassium sodium ratio 0 11) was 16 months The median duration of life of rats eating 8 4% sodium chloride and 4 7% potassium chloride (potassium sodium ratio 0 8) was 24 months about the same as that of controls The increase in median duration of life was 8 months The effect on survival of adding 2 9% potassium chloride to the 5 6% sodium chloride ration was equally great the median duration of life being increased 7 months Animals receiving extra potassium chloride in the 5 6% sodium chloride ration outlived controls by several months suggesting that the control diet was suboptimal in potassium sodium or both

There are at least two kinds of hypertension in animals eating excess sodium chloride (1) moderate hypertension associated with moderately high levels of increased sodium chloride intake which is not ameliorated by increased potassium feeding and (2) high hypertension associated with high levels of sodium chloride feeding which is moderated to intermediate levels by extra potassium chloride

► [The fact that hypertensive patients characteristically excrete more sodium in their urine than normal control patients has raised a question as to whether the increased sodium intake is itself responsible for either producing or aggravating the blood pressure elevation It seems equally

sons disliked the flatness of food taste for a few days or weeks but thereafter this was no problem This suggests that the salt appetite was acquired in these persons and that among those with hypertension it was not a symptom of the disease and among those without hypertension it was not a physiologic response to need

Experimental Epidemiology of Chronic Sodium Chloride Toxicity and Protective Effect of Potassium Chloride George R Meneely and Con O T Ball (Vanderbilt Univ) tested the effect of varying sodium chloride intake on 191 rats divided into 6 groups of 30 each and 1 group of 11 The last group ate the basic ration which contained only 0 01% sodium chloride This amount of sodium chloride proved to be suboptimal as evidenced by anorexia diminished growth and decreased survival rate

The diet consumption of the animals eating higher levels of salt was slightly greater Water consumption was essentially proportional to dietary sodium chloride up to 8 4% but above this no further increase in fluid intake occurred Urine formation paralleled the fluid intake Growth was inversely affected by salt intake each increment of salt producing a small but consistent decrement in weight gain This impaired growth persisted throughout life

From the 2d to 6th month of this experiment and at the same time and at the same per cent incidence in all similar experiments there occurred sporadically among rats eating 7% sodium chloride or over a nephrosis like syndrome Onset of edema was abrupt and massive The other important features were hypertension in most animals anemia pronounced lipemia severe hypoproteinemia and azotemia All animals with this disorder died usually in the edematous phase less often after loss of edema and development of cachexia All animals showed severe arteriolar disease

The disturbed lipid metabolism was characterized by hyperlipemia and lipid deposits in arterioles throughout the body and in the renal parenchyma Serum cholesterol levels tended to increase with increasing dietary sodium chloride but more striking was correlation between serum cholesterol level and the observed level of the blood pressure Elevated cholesterol levels did not occur in normotensive animals

( ) Am J Med 2 713 7 N mbe 19 8

but more patients and scientific data are necessary for study before the findings can be accepted as representative of a new syndrome Although the routine renal investigations are normal presence of parenchymal disease yet to become manifest must be ruled out

Observations on Carbon Dioxide Tension during Recovery from Metabolic Acidosis were made by Robert W Winters John A Lowder and Nelson K Ordway[7] (Univ of North Carolina) in children and adults with diabetic diarrheal or uremic acidosis Most patients recovering from diabetic acidosis passed through a point at which the pH was normal or elevated but the plasma carbon dioxide tension (Pco_2) depressed Delayed return of Pco to normal was noted in patients recovering from diarrheal or uremic acidosis published observations by other workers on persons recovering from ammonium chloride acidosis showed a similar pattern

The lower than normal Pco_2 values suggest that hyperventilation is in some measure sustained—a contention supported by ventilation measurements reported by other workers The mechanisms underlying continued hyperventilation by such patients are not clear It is apparent that within the confines of Gray s multiple factor theory for the chemical control of pulmonary ventilation no stimulus is discernible in the arterial blood for the augmented ventilation since Pco is reduced hydrogen ion is normal or reduced and Po presumably elevated because of hyperventilation

One explanation might be that the sensitivity of the respiratory center to Pco and/or hydrogen ion has been increased Increased sensitivity assessed by a change in the slope of the curve relating the alveolar ventilation ratio to arterial Pco_2 during inhalation of various concentrations of carbon dioxide has been demonstrated in other situations in which there has been sustained hypocapnia but with alkalosis viz passive hyperventilation of normal persons and acclimatization to high altitude The opposite response decreased sensitivity to Pco has been adequately demonstrated in chronic hypercapnic states

The mechanisms mediating increased sensitivity of the respiratory center are not understood

► [These observations may explain the clinical finding of patients who on

[7] J Cl In t 37 640 645 M y 1958

possible howeve that the increased sodium excretion is a result of the hypertension and that the increased sodium intake is a response to an increased demand for this ion Meneely s experiments (as well as those of many others including Selye Knowlton Perera Tobian etc) suggest that the salt changes are primary but the amount of sodium given in Meneely s experiments is much larger than the quantity human beings usually take Until the mechanism of the relation of sodium to hypertension is more clearly defined this question will remain open —Ed]

Salt Wasting Syndrome in Infancy is reported by Donald B Cheek and John W Perry[6] (Royal Children s Hosp Melbourne) Continued loss of sodium and chloride is a well known phenomenon occurring during uncontrolled adrenal insufficiency In children such losses lead to failure of growth and development asthenia and infection As it is well recognized that many symptoms of adrenal insufficiency are due to disturbance in mineral metabolism it is not surprising that other conditions in which excessive amounts of salt are lost from the body occasionally give rise to a picture in many respects resembling adrenal insufficiency

A renal salt wasting defect was noted in an infant who failed to thrive and to maintain hydration satisfactorily Adrenal and kidney function and acid base balance were normal Low sweat electrolyte levels indicated adequate production of mineralocorticoid The deleterious clinical situation was reversible by raising the serum concentration to normal by addition of 5 Gm sodium chloride to the milk intake When the infant was off salt or on desoxycorticosterone acetate (DCA) only the serum sodium concentration extracellular volume and total chloride value fell or were low and the clinical condition deteriorated The urinary sodium potassium ratio was not affected by DCA

If electrolyte concentration of sweat is a satisfactory index of endogenous mineralocorticoid production then the salt wasting condition in this infant is not due to adrenal insufficiency but may be related to a transient disturbance in response of the renal tubules to this type of hormone

Payne believed that a renal tubular salt wasting condition occurs in infancy and that it is resistant to DCA He stated that such a condition can for a time threaten the life of an infant but that after several weeks spontaneous recovery occurs He believed that the condition was not related to adrenal insufficiency The authors support this contention

(6) A ch Dis Childhood 33 252 256 J ly 1958

The relative ineffectiveness of mercuric chloride when compared with that of organic mercurials has previously been considered a evidence against the thesis that the di uretic activity of the organic compounds is attributable to the mercuric ion itself However the argument loses valid ity by the demonstration that the mercuric cysteine complex is more potent than the organic mercurials thus far tested

Chronic Potassium Depletion Due to Purgation with Cascara is reported by B J Houghton and M A Pears[9] (St Mary s Hosp London)

Woman 55 was hospitalized for weakness diarrhea anorexia nausea and vomiting For 5 years she had taken 10 15 gr cascara sometimes even more usually about 2 or 3 times a week In each fol lowing day or 2 days she had passed 2 4 copious fluid or semiformed stools She looked pale and tired The legs were o weak that she was unable to lift them or to flex the hips Superficial and deep sensation was normal

Blood values were urea nitrogen 41 mg and total proteins 5 5 Gm /100 ml sodium 141 potassium 1 7 and chloride 111 mEq /L and total carbon dioxide 18 6 mM /l Urinary potassium level was 4 mEq /L An ECG showed the sagged S T segments wide inverted T waves prolonged Q T interval and U waves characteristically seen in hypokalemia

The patient was placed on replacement therapy by intravenous drip with 4 Gm potassium chloride in each liter of 5% dextrose in water After 24 hours of therapy she showed dramatic improvement By that time she had retained 148 mEq potassium and plasma potas sium level was 2 3 mEq /L

After 48 hours of treatment 8 7 Gm dipotassium hydrogen phos phate was substitut d for pota sium chloride in the drip because in view of the potassium depletion deficiency of phosphate might co exist Within a few hours tetanic symptoms developed and K_2HPO_4 was discontinued

On the 5th day after beginning treatment the plasma total carbon dioxide had fallen still further to 14 9 mM /L It was believed that this fall in the plasma bicarbonate level might indicate the movement of hydrogen ions out of the cells which were taking up potassium i e the converse of the process which has been postulated during de velopment of potas ium depletion Therefore 2°0 mM sodium bicar bonate in i otonic solution was given during the next 48 hours at the end of which time the plasma total carbon dioxide had risen to 24 3 mEq /l

The course thereafter was uneventful and 9 days after treatment had started he had retained 795 mEq potassium Plasma potas ium level was 6 5 mEq /L and in the last 24 hours of the balance study she pa sed 1 000 ml urine containing 44 mEq potassium The ECG had returned to normal and she felt well

► [The importance of the cathartic habit (as above) or dietary idiosyn

(9) Brit M J 1 13 8 1330 J 7 1 8

recovery from diabetic acidosis continue to have a depressed plasma CO after ketosis has cleared —Ed]

Effects of Acid Base Balance on Diuresis Produced by Organic and Inorganic Mercurials were studied by two approaches by Robert I Levy I M Weiner and Gilbert H Mudge[8] (Johns Hopkins Univ) with the technical assistance of Florence Risser Charlotte Bills and Sally Renshaw First the effects of varying doses of meralluride and a mercuric salt mercuric cysteine on chloruresis were compared in normal acidotic (NH_4CL) and alkalotic ($NaHCO_3$) dogs The mercuric salt is a much more potent chloruretic and is influenced to a much smaller extent by changes in acid base balance than is meralluride This finding indicates that a major part of potentiation by acid forming salts is related to the relative ease of release of mercuric ions from organic mercurials in acid mediums

Second dogs received hypertonic infusions which kept plasma chloride concentration and glomerular filtration rate elevated whereas the acid base balance was varied by infusion of other anions i e nitrate sulfate and bicarbonate Under these circumstances with almost identical chloride load bicarbonate inhibited the mercurial effect but nitrate and sulfate did not This finding emphasizes the role of pH in determining mercurial effectiveness

If the diuretic action of mercurials involves a pH dependent reaction does this occur in the cells of the kidney or in the urine within the tubule? Our knowledge of renal intracellular pH is so fragmentary and so indirect that this question cannot be answered at present Since the electrolyte metabolism of the kidney is so different from that of other tissues it would appear unreasonable to attempt to define renal mechanisms by extrapolation from other tissues It is generally believed that the site of mercurial action is on the tubular cell or on its membrane and there is good evidence that mercurials are taken up by the cells of the kidney and thence secreted into the tubular urine Hence it might be logical to conceive of a pH dependent reaction as occurring within the cell itself However there is no a priori reason why the rupture of a carbon to mercury bond could not occur within the tubular urine This might then be followed by a subsequent reaction between mercuric ions and the immediately adjacent cellular membrane

(8) J Clin I et 37 1016 10 3 J ly 1958

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(8) J Cl I i 37 1016 10 3 J ly 1958

potassium deficiency This derangement is in addition to the well known abnormality of renal tubular function found in human beings and animals whose potassium stores have been depleted A somewhat similar observation was made by *Fourman and Leeson (Lancet 1 268 Feb 7 1959)* who found that a patient with severe potassium depletion suffered from impaired thirst perception Since thirst and the release of vasopressin are closely related in normal persons the mechanisms may be similar —Ed.]

Changes in Serum Potassium Level and in pH of Arterial Blood in Respiratory Acidosis were studied by H Priscilla S Foulds David Mendel and Robert R de Mowbray[2] (St Bartholomew s Hosp London) in 16 men aged 49 66 with

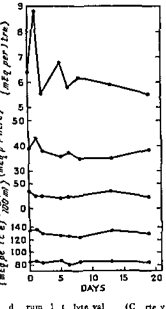


Fig 91 —Blood and serum electrolyte values (Courtesy of Foulds H P S et al Lancet 1 405 409 Feb 22 1958)

chronic bronchitis and emphysema Serum potassium levels were over 5 5 mEq /L in 7 Of the 7 5 were acutely ill with respiratory infection In 3 potassium levels of 7 mEq /L or over were recorded they were the most severely ill patients and presented a clinical picture of carbon dioxide narcosis

Man 64 with bronchitis in the winter for 3 years and increasing breathlessness for 3 weeks was hospitalized for emphysema and acute exacerbation of chronic bronchitis without congestive failure Blood

(2) Lancet 1 405-409 Feb 22 1958

crasies (as below) in causing potassium depletion is often overlooked.
—Ed.]

Contributory Role of Extrarenal Factors in Polyuria of Potassium Depletion was observed by Charles R. Kleeman and Morton H. Maxwell[1] (Univ. of California, Los Angeles).

Man, 68, was hospitalized because of progressive fatigue, weakness and drowsiness of 6 months and increasing nocturia, polyuria and polydipsia of about 3 months' duration. He had taken 5-10 oz. of milk of magnesia daily for 10 years and had added 2 enemas daily to the cathartic regimen for the preceding 6-8 months. For the last 2-3 months his diet consisted mainly of cottage cheese and applesauce. Aside from dehydration, profound weakness and hypoactive deep tendon reflexes, the examination was negative. The ECG was consistent with hypokalemia. Serum potassium concentration was 2.5 mEq./L., accompanied by hypochloremic alkalosis.

He received 155 mEq. potassium daily in addition to that in the diet (total about 200 mEq./day) for the 1st hospital week, and he retained about 900 mEq. during this period. The hypokalemia and alkalosis were rapidly corrected, and 5 days after therapy was begun a temporary hyperkalemia and mild acidosis developed. The very low urinary excretion of potassium during the 1st few days of therapy confirmed the extrarenal origin of the potassium depletion. The concentration of this ion in the urine reached a minimum of 4 mEq./L. on the 2d hospital day.

Although the potassium replacement therapy resulted in prompt and marked clearing of the sensorium and muscle strength, there was little early improvement in abnormal water metabolism. The polyuria continued.

Since it was apparent that the patient, when dehydrated, was unable to form a hypertonic (or even isotonic) urine except on the 4th day, when aqueous vasopressin was administered, an intravenous concentration test was performed on the 9th day. The urinary osmolality rose to 548 mOsm./kg. of urinary water during the test, but 2 hours after infusion of vasopressin was stopped it had fallen to 200 mOsm./kg. In view of these responses to antidiuretic hormone, therapeutic doses of aqueous vasopressin were administered from the 9th through the 20th day, with a trial withdrawal on the 12th and 13th days. This therapy resulted in a moderate but distinct reduction in the 24-hour urinary volumes. The patient refused additional injections of vasopressin; urinary volumes ranged between 4 and 5 L./day. He left the hospital with instructions to take a regular diet and refrain from cathartics and enemas.

After about a year without enemas or cathartics and with proper diet, polyuria had progressively decreased to 1-2 L./day. He conserved sodium normally and formed an acid urine (pH 4.5) when challenged with a diet containing 200 mg. sodium and ammonium chloride, respectively. Renal conservation of potassium was normal on a low potassium diet.

► [The implication of this paper is that the regulation of release of the antidiuretic hormone may be deranged in patients with severe chronic

(1) New England J. Med. 260: 68-271, Feb. 5, 19[illegible]

nalectomized Unanesthetized Dogs Effect on Electrolyte and Water Excretion was studied by A C Barger R D Berlin and J F Tulenko[3] (Harvard Med School) A technic was used for chronic catheterization of one renal artery with collection of urine from each kidney individually In the normal dog intrarenal arterial infusion of aldosterone or 9α fluorohydrocortisone produced unilateral kaluresis but no demonstrable natriuresis or effect on water excretion In the same catheterized dogs after recovery from adrenalectomy small doses of aldosterone infused into the renal artery produced unilateral antinatriuresis The unilateral kaluresis was of the same magnitude as that observed in the normal state In the normal and adrenalectomized animals the effect of intrarenal aldosterone on potassium excretion was apparent only after a delay of 30 60 minutes maximum effect was noted after 2 3 hours

This investigation also clearly indicates local renal action of antidiuretic hormone on water excretion and rapidity of its action No natriuresis was observed with antidiuretic hormone in normal dogs on water diuresis

► [It is important that Barger s dogs did not respond for at least 30 minutes after the direct application of aldosterone to their kidneys This makes it clear that an acute increase of aldosterone secretion could not account for the diminished sodium excretion which occurs abruptly in human beings when they assume an erect posture or after the application of tourniquets The response of dogs is certainly not slower than that of human beings since Ross and co workers report a latent period of at least 2 hours before effects on urinary sodium or potassium excretion were observed in persons with Addison s disease given aldosterone intravenously (J Clin Endocrinol 19 289 1959) —Ed]

Clinical Studies on Control of Sodium and Water Metabolism in Panhypopituitarism were made by Andre Lanthier and C E Grignon[4] (Notre Dame Hosp Montreal) Control of sodium and water metabolism in absence of anterior pituitary function is still not completely understood The syndrome of hyponatremia in panhypopituitarism has been attributed by some authors to water retention Others have claimed a defective mechanism for renal conservation of sodium due to lack of increased adrenocortical secretion of aldosterone in response to sodium deprivation in absence of adequate anterior pituitary function In a patient with panhypopituitarism and hyponatremia it was noted that hyponatremia which may be produced by dietary sodium re

(3) E doc 1 gy 6 804 815 J 1958
(4) Am J M S 36 353 360 S pt mb 19 8

pressure was 145/80 mm Hg The ECG showed tall P waves Later radiography of the chest showed bronchopneumonia

When placed in an oxygen tent he became convulsive and mentally confused He had severe continuous headaches and papilledema Cyanosis relieved when he was placed in the tent recurred on his removal from it The 2d day of treatment in the tent a random sample of venous blood gave the following serum levels potassium 6 4 sodium 135 chlorides 84 and CO_2-combining power 39 mEq /L and urea 36 mg /100 ml (equivalent of a blood urea nitrogen level of 18 mg /100 ml) The next day serum potassium level was 8 8 mEq /L During the next week throughout which he was in the oxygen tent serum potassium levels and CO -combining power fluctuated but tended to fall (Fig 91) His mental state gradually returned to normal and convulsions subsided The blood urea level remained normal throughout On the 23d day of hospitalization when he had been out of the oxygen tent for 12 days he had a sudden attack of dyspnea and died within 45 minutes Autopsy revealed early bronchopneumonia severe emphysema moderate right ventricular hypertrophy and dilation and congestion of liver spleen kidneys and brain

In 3 patients serum potassium levels rose rapidly during oxygen therapy In 1 of the 3 this change was associated with rapid decrease of the pH of the arterial blood another showed a slight rise in serum potassium level with increase of pH due to hyperventilation

The rise in serum potassium level probably represents transfer of potassium from the cells to the extracellular fluid This may be due to an increased Pco and experimental evidence suggests that the potassium may be liberated from the muscles This is not the only mechanism however because the serum potassium level may also rise slightly during hyperventilation Impaired renal function may also be a factor

Rapid rises of extracellular potassium concentration might contribute to unexplained sudden deaths that occur in cor pulmonale The possibility of carbon dioxide narcosis as a result of intensive oxygen therapy is well recognized That hyperkalemia occasionally develops under these conditions may be further reason for caution in administration of oxygen

► [An additional lesson from this report is the possible danger of administering acidifying agents such as ammonium chloride or acetazolamide (Diamox®) to patients with *acute and decompensated* respiratory acidosis —Ed.]

Infusion of Aldosterone 9α Fluorohydrocortisone and Antidiuretic Hormone into Renal Artery of Normal and Adre

tate or aldosterone but it can usually be corrected by hydrocortisone like steroids

Nonhormonal factors have recently been shown to be important in water diuresis in normal subjects The rate of glomerular filtration and solute excretion and the distribution of the reabsorbed solutes between the proximal and distal tubules can profoundly alter the diuretic response to water in the absence of antidiuretic hormone To test this effect in patients with pituitary and adrenal insufficiency Charles R Kleeman Morton H Maxwell and Robert E Rockney[5] performed 16 experiments on 12 men—8 with anterior pituitary insufficiency and 4 with primary adrenal insufficiency Aminophylline or Mercuhydrin® was used to increase glomerular filtration acutely and alter the tubular reabsorption of solute The effect was compared in the same subject with that after subsequent administration of hydrocortisone

The impaired water excretion was partially corrected by aminophylline or mercurials but hydrocortisone caused a much greater improvement in all the characteristics of the water diuresis The ability of aminophylline to improve the water diuresis—a decrease in osmolality and an increase in the free clearance of water—of the patients excreting a moderately hypertonic urine is readily explained by its effects on glomerular filtration rate and solute excretion The increase in filtration rate and the inhibition of solute reabsorption in the proximal tubule greatly enhanced the delivery of isosmotic fluid into the distal or diluting segment Here in the absence of the antidiuretic hormone a greater volume of hypotonic fluid would be formed When this volume is decreased by reabsorption of an absolute fixed quantity of water in a terminal concentrating segment the ultimate effect is production of a greater amount of more dilute urine than that excreted in the control periods

Aminophylline and Mercuhydrin® by increasing glomerular filtration rate and/or solute excretion partially correct the impaired water excretion in patients with adrenal and pituitary insufficiency The marked improvement after hydrocortisone however cannot be explained solely by these mechanisms The steroid probably acts primarily by inhibiting the back diffusion or reabsorption of water in the loop of

(5) J Cl I st 37 1799 1808 D mb 1958

striction in patients with untreated panhypopituitarism was primarily due to water retention resulting from decreased secretion of 17 hydroxycorticosteroids

The authors consider a possible interrelation among 17 hydroxycorticoids antidiuretic hormone and renal handling of water Patients with untreated Addison s disease show delay in elimination of a water load which may be corrected by cortisone Patients with untreated panhypopituitarism also show the same delay which may be corrected by ACTH or cortisone as in the authors patient Often it is also possible to elicit diuresis in edematous patients with 17 hydroxycorticoids It is clear that there is a definite influence of 17 hydroxycorticoids on the renal control of water balance Apparently 17 hydroxycorticoids do not inhibit ADH and do not have a competitive action antagonistic to ADH on the kidney The possibility that 17 hydroxycorticoids may diminish the secretion of antidiuretic hormone has been suggested but cannot be considered at the moment because of lack of a reliable method of measurement However it seems certain that 17 hydroxycorticoids may increase the renal elimination of water by a direct action on the kidney without any relation to antidiuretic hormone This direct renal action of 17 hydroxycorticoids may be due either to an increase in the glomerular filtration rate or to a decrease in the distal tubular reabsorption of solute free water or to a combination of both mechanisms

► [An occasional patient with long standing hypopituitarism may be unable to conserve sodium on a salt free diet because the adrenals have become atrophic and can no longer produce adequate amounts of aldosterone More often the development of hyponatremia in hypopituitary states is secondary to retention of water as in the above case report In such instances sodium is wasted in the urine despite hyponatremia in a manner analogous to that described by Leaf *et al* (J Clin Invest, 32 868 1953) in normal subjects in whom water retention was induced by injections of antidiuretic hormone Such salt wasting' cannot be avoided by increasing the maintenance dose of salt retaining' *hormones (such as desoxycorticosterone or fluorocortisone) but can be overcome by increasing the intake of cortisol or restricting water* —Ed]

Mechanisms of Impaired Water Excretion in Adrenal and Pituitary Insufficiency I Role of Altered Glomerular Filtration Rate and Solute Excretion Animals and humans with impaired adrenal or pituitary function cannot excrete a water load normally This defect persists in the presence of normal salt balance normal extracellular volume and an adequate supply of salt retaining hormone desoxycorticosterone ace

Urinary sodium excretion then assumed a cyclic pattern with peaks of excretion and retention every 4 5 days Potassium excretion was increased throughout the period of aldosterone administration Renal function and excretion of 17 ketosteroids and 17 hydroxycorticosteroids were unaffected

These findings are consistent with the lack of edema in primary aldosteronism Sodium excretion during volume loading need not be related to diminished aldosterone secretion The mechanism of this escape from sodium retention during continued administration of aldosterone or other salt retaining corticosteroids is not understood

► [This important paper demonstrates for aldosterone what was already abundantly clear for desoxycorticosterone (see Perera Proc Soc Exper Biol & Med 68 48 1948) i e that continued administration of large amounts of the steroid does not produce edema in normal persons This could perhaps have been deduced from the fact that patients with hyperaldosteronism due to tumors do not have edema unless congestive heart failure develops late in the course of their disease This observation however raises a serious problem in interpreting the importance of aldosterone in production of edema whether in congestive heart failure cirrhosis or the peculiar periodic edema sometimes seen in women which is often accompanied by increased excretion of aldosterone in the urine (Luetscher Tr A Am Physicians 57 158 1957)

Another difficulty in explaining the edema of heart failure as a result of aldosterone hypersecretion is outlined in the next paper Apparently hypersecretion need not occur in patients with this type of edema!—Ed]

Isolation of Urinary Metabolite of Aldosterone and Its Use to Measure Rate of Secretion of Aldosterone by Adrenal Cortex of Man In the past the only index of aldosterone secretion has been measurement of the small fraction of unchanged hormone which appears in the urine In the method devised by Stanley Ulick John H Laragh and Seymour Lieberman[7] (Columbia Univ) 1 µg aldosterone containing 500 000 cpm d aldosterone H^3 is injected intravenously the 24 hour urine collected and the aldosterone metabolite isolated for determination of its specific activity The amount of aldosterone produced during the day is calculated by dividing the total counts per minute of aldosterone injected by the specific activity of the metabolite Isolation of the metabolite from extracts of glucuronidase hydrolyzed urine requires three chromatographic separations It is not necessary to determine the total amount of metabolite in urine but only to isolate a measurable portion and determine its tritium content *per microgram*

(7) T A Am Phy 71 25 235 1958

Henle the distal tubule or the concentrating segment in the absence of circulating antidiuretic hormone

► [It appears that hypopituitarism affects water excretion both by altering glomerular filtration and by altering tubular function The importance of the reduced solute load presented to the kidneys of the patient with pituitary insufficiency as compared with the normal individual has been discussed by Leaf (J Clin Invest 31 914 1952) but now it appears that this effect although of considerable importance is not the only factor modifying the ability of the kidneys of patients with adrenal or pituitary insufficiency to respond to a water load —Ed]

Response of Normal Subjects to Large Amounts of Aldosterone Exogenous aldosterone in man causes sodium and chloride retention and potassium excretion Increased amounts of this hormone appear in the urine of patients with sodium retention associated with cardiac failure cirrhosis and nephrosis and during sodium or fluid depletion Decreased aldosterone excretion has been found with increased urinary sodium excretion during extracellular fluid volume expansion and conversely increased aldosterone excretion has been found with decreased urinary sodium excretion in extracellular fluid volume depletion These findings indicate that aldosterone is important in fluid and electrolyte metabolism However patients with primary aldosteronism have no marked sodium retention and no edema

J Thomas August Don H Nelson and George W Thorn[6] (Harvard Med School) carried out extensive studies in 2 healthy men aged 28 and 30 One received aldosterone intramuscularly 3 mg daily for 14 days the other received 3 mg daily for 4 days then 6 mg daily for 22 days The diet remained constant

In both subjects the results were similar to those previously reported with long term administration of desoxycorticosterone acetate Maximal weight gains did not exceed 3 5 kg and 3 kg sodium and water retention occurred for only a few days and significant edema did not appear Arterial diastolic blood pressures increased 10 20 mm Hg with maximal weight gain and remained elevated until the drug was discontinued

During aldosterone administration sodium excretion suddenly increased—in 1 subject on the 5th day when the cumulative weight gain was 1 5 kg and cumulative sodium retention was 270 mEq and in the other on the 16th day when weight gain was 3 kg and sodium retention 536 mEq

(6) J Clin Invest 37 1549 1555 November 1958

congestive heart failure hypersecretion of aldosterone was not demonstrated

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THE THYROID GLAND

Central Regulation of Thyrotropic Activity of Anterior Pituitary Functional Importance of Nucleus Medialis Habenulae was studied by J Szentagothai and B Mess[8] (Univ of Pecs) In test animals bilateral destruction of the nuclei habenulae curbed the goitrogenic effect of small doses of thiouracil In endemic goiter areas development of goiter was prevented in albino rats by adding iodine or thyroxin to the diets The goiter in the rats also disappeared after symmetrical destruction of the nuclei habenulae

In test animals thyroidectomy was followed by decrease of the thyroid stimulating hormone (TSH) in the anterior pituitary and its increase in the serum After destruction of the nuclei habenulae transfer of TSH from the anterior pituitary into the blood stream was greatly decreased Administration of thyroxin caused inactivation of the thyroid gland in the test animals by curbing TSH production and secretion in the anterior pituitary In albino rats with bilateral destruction of the nuclei habenulae administration of thyroxin caused much less inactivation of the thyroid gland

Obviously intact nuclei habenulae are not indispensable for the self steering mechanism of the TSH thyroxin system as large doses of thiouracil or thyroxin exerted about the same effect on intact animals as on those with the nuclei habenulae destroyed It appears that the neural role played by these nuclei serves to compensate only for slight imbalances in the TSH thyroxin system It may be assumed that slight deviations in the thyroxin blood level affect the TSH secretion only through the intact nuclei habenulae while greater deviations affect the anterior pituitary directly

It was experimentally demonstrated that thyroxin does not affect the nuclei habenulae directly However its indirect effect is documented by the fact that both thyroidectomy and thiouracil administration lead to significant decrease in the nuclear *volume of the nucleus medialis habenulae Since the*

(8) W kl W b sch 70 258 1 Ap 11 1958

Normal subjects on unselected diets have been found to secrete 150 300 μg aldosterone daily When a normal subject was depleted of sodium and developed a negative balance of 150 mEq aldosterone secretion increased to 930 μg In another subject addition of 10 Gm NaCl daily for 5 days led to a decrease in aldosterone secretion from 250 to 50 μg In normal subjects aldosterone secretion may vary from 50 to almost 1 000 μg /day under the influence of changes in sodium intake alone

Patients with hepatic cirrhosis and ascites had consistently marked hypersecretion of aldosterone during a balance

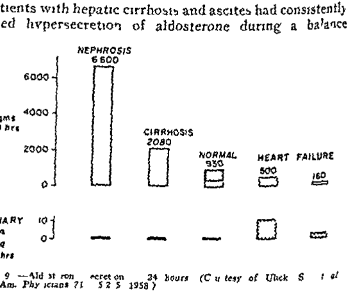


Fig 9 —Ald st ron ecret on 24 hours (C u tesy of Ulick S t al Tr A Am. Phy icians 71 5 2 5 1958)

study and the feeding of NaCl did not depress its secretion Hypersecretion was also found in the edematous phase of the nephrotic syndrome Two patients with chronic heart failure and marked peripheral edema and ascites despite rigorous medical measures had aldosterone production of 500 and 160 μg respectively neither amounts being considered hyper secretion The urine sodium values were markedly low except in the patient with congestive failure and the relatively high aldosterone production (Fig 92)

The finding of marked hypersecretion of aldosterone in hepatic cirrhosis and in the nephrotic syndrome agrees with the results obtained by measuring the excretion of biologically active aldosterone in urine However in 2 patients with

produced by these quantities Hormonal release was also unaffected by administration of thyroxin

The 2 patients in the euthyroid stage of Graves disease and 1 with acromegaly and hyperthyroidism were also unaffected by triiodothyronine

Previous studies had shown that radioiodine uptake which is increased in patients with Graves disease is not inhibited by administering thyroid hormone The present studies indicate that hormone release by the gland is likewise not inhibited in such patients when thyroid hormone is given The failure of large doses of triiodothyronine or thyroxin to suppress the thyroidal secretion rate in patients with hyperthyroidism strongly favors the concept that either the thyroid gland or the suprathyroidal regulatory system is functioning autonomously and that the disorder of regulation i qualitative rather than simply a quantitative abnormality

Effect of Iodide on Action of Thyrotropin in Hypophysectomized Patient Richard S Benua and M B Lipsett[1] (New York) tried to determine whether administration of iodide can alter the acceleration of the discharge rate produced by thyrotropin in hypophysectomized patients Such patients are ideal subjects for the study of the effect of iodide on the action of thyrotropin since endogenous sources of this hormone are excluded

Six previously euthyroid hypophysectomized patients were given thyrotropin by injection twice daily to stimulate thyroidal uptake and secretion of radioactive iodine In the presence of a goitrogen induced block of organic binding of iodine and during continued administration of thyrotropin iodide produced a significant decrease in the rate of loss of I^{131} from the thyroid gland in only 1 patient Propylthiouracil without thyrotropin did not increase the rate of loss of I^{131} from the thyroid of a hypophysectomized patient Thyrotropin was used in a dosage of 10 units/day in 4 studies and 2 units/day in 3 studies The rate of loss was less with 2 units than with 10 units whether or not iodide was administered

Iodide decreased significantly the rate of loss of radioiodine from the thyroid in 2 separate studie on the same hypophysectomized patient This effect of iodide on the action

volume of the nerve cell nuclei is characteristically related to their function the volume changes in the nucleus medialis habenulae clearly indicate the functional effect of the thyroxin blood level on this nucleus

► [The importance of the hypothalamus in controlling the release of thyroid stimulating hormone has been discussed previously (1958 59 YEAR BOOK p 631) This study pushes the controlling centers for the release of thyroid hormone still higher into the brain but it appears that the higher centers exert less direct control than the lower ones In this respect *it is of interest that Yamada and Greer (Endocrinology 64 559 1959)* found that thyroxin suppressed the release of thyroid stimulating hormone much more rapidly if injected directly into the pituitary than if injected into the TSH control center of the hypothalamus --Ed]

Effect of Triiodothyronine and Thyroxin on Rate of Release of Thyroid Hormone in Various Thyroid States Delores E Johnson David H Solomon and Monte A Greer[9] studied 12 normal subjects 15 patients with hyperthyroidism 2 in the euthyroid stage of Graves disease and 1 acromegalic patient with hyperthyroidism Diagnoses were unequivocal by the usual clinical and laboratory criteria

Thyroidal secretion rate was determined by external scintillation counting over the thyroid gland following administration of 25 300 μc I^{131} Reutilization of I^{131} liberated *from the thyroid gland was prevented by giving 30 60 mg* methimazole every 6 8 hours after maximal uptake of radioiodide had occurred The slope of the semilogarithmic curve described by serial counts over the neck represents the fractional rate of release of hormone from the thyroid gland corrected for physical decay of the I^{131} source

The normal subjects received 75 100 μg triiodothyrone per day All showed partial to complete inhibition of hormonal release demonstrated by flattening of the release curve within 24 hours and rebound when the triiodothyronine was stopped One subject who received 6 mg thyroxin over a 24 hour period demonstrated immediate and sustained flattening of the release curve for 14 days then a gradual return to the base line by 30 days after administration of the thyroxin

In contrast the patients with hyperthyroidism showed little or no change in thyroidal secretion rate when triiodothyronine was administered in doses up to 1 600 μg /day Definite elevation of the basal metabolic rate was usually

(9) J Cl E docri ol 19 317 329 Ma h 1959

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(1) J Cl E d 1 19 19 27 J ry 1959

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If it be assumed that the thyroid gland of the normal hu man subject is in a steady state with regard to iodide uptake hormone formation and hormone secretion then the admin istration of iodide must produce either hyperthyroidism or a decrease in one or more of the rate constants describing these functions of the gland It is suggested that one of the control *mechanisms may be an iodide inhibition of the* action of thyrotropin on the gland It is impossible to determine whether iodide acts on the thyrotropin in the blood at the thyroid gland or on some intrathyroidal system controlled by thyrotropin

► [These data should have helped clarify the discrepancies between the data of Greer and DeGroot as compared with those of Solomon (1957 58 YEAR BOOK p 638) Unfortunately the ability of iodine to block exoge nous thyroid stimulating hormone could be demonstrated in only 1 patient so the question remains somewhat unsettled The fact that TSH can be blocked by iodine in some instances however suggests that with proper conditions it might be possible to demonstrate a block in all cases —Ed]

Presence of Abnormal Thyroid Stimulating Hormone in **Serum of Some Thyrotoxic Patients** was investigated by D D Adams (Dunedin New Zealand) The content of thy roid stimulating hormone (TSH) in some human serums has been found to induce abnormal responses in the TSH assay The assay method entails measurement of the effect of TSH in releasing I^{131} from thyroid glands of thyroxin injected guinea pigs Release of I^{131} from the thyroid of the guinea pig is measured by following the increase of plasma I^{131} concentration in the animal In the normal response the *I^{131} level in the plasma of the guinea pig* is higher at 3 than at 16 hours after intravenous injection of TSH In the ab normal response elicited by serums from some patients with thyrotoxicosis the reverse occurs the plasma I^{131} level of the guinea pig being higher at 16 than at 3 hours after intra venous injection of the serum

The mechanism of the abnormal response and the type of response elicited by *the TSH present in human* bovine and

( ) J Cl Endoc 1 18 699 712 J ly 1958

rat pituitary glands and in the blood of thyroidecto mized rats and a variety of human subjects were studied When USP thyrotropin reference substance was added to a serum that elicits the abnormal TSH response magnitude and time course of the response induced by the mixture in dicated that the two components act independently

The size of the abnormal response was not reduced by in jecting into the test guinea pig a massive dose of thyroxin Therefore it is unlikely that the abnormal TSH response is due to blockage of thyroxin inhibition of endogenous TSH *secretion from the pituitary gland of the test guinea pig* This does not exclude the po sibility that the abnormal response is due to stimulation of the pituitary of the guinea pig but it seems most likely that the action is directly on the thyroid

Because the action of standard TSH was not affected by its addition to a serum eliciting the abnormal response this response cannot be attributed to interference with the ac tion of normal TSH Thus it is probable that the respon e is a manifestation of the presence of an abnormal TSH The finding of abnormal responses only to serums from patients with thyrotoxicosis indicates that the abnormal TSH has some relation to this disorder However the possibility that abnormal TSH may occur in conditions other than thyrotox icosis cannot be excluded

It has been shown that serums from some patients with exophthalmos and hyperthyroidism have the power to in crease markedly the acinar cell height of the thyroid glands of thyroxin injected guinea pigs It is likely that these se rums contained the abnormal TSH which apparently affects thyroid morphology similarly to normal TSH It may be that abnormal TSH differs from the normal in length of stay in the blood Possibly it is normal TSH combined with some other material The site of production of abnormal TSH remains unknown

► [These observations have been confirmed by McKenzie (Endocrinology 62 865 1957) When one compares the time effect curves of normal thyroid stimulat ng hormone with those of the abnormal component de scribed by Adams it becomes clear that previous attempts to demonstrate TSH in the blood or urin of patients with Graves disease would prob ably have missed this component because it has hardly begun to act at a time when ordinary TSH reaches its peak It seems that all previous at tempts to study thyro d stimulating activity of body fluids in thyro d d s ease will have to be repeated Meanwh le where does this special TSH come from?—Ed]

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(2) J Clin Endocrin 18 699 712 July 1958

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(2) J Clin Endoc 1 18 699 712 July 1958

Reserpine has often been used without ill effect on patients with normal or even low arterial pressure The pulse rate became normal in all with appearance of bradycardia in 1 patient Goiter present in 8 patients was favorably influenced in only 1 this was a discrete recent thyroid hyperplasia Diffuse vascular goiters lost their pulsations but their size was not changed Old nodular goiters remained unchanged Exophthalmos was improved in 3 of 6 patients Diarrhea was relieved by reserpine in 1 patient in whom this was the dominant symptom Loss of weight was arrested in all but 1 patient in fact weight gains of 1-4 kg were recorded The BMR decreased in all patients in 3 the decrease was spectacular—+44 to +14% +52 to +4% and +57% to +16%

In the prolonged therapy group a woman 29 with purely endocrine hyperthyroidism was given 0 75 mg /day for 2 months The drug had an excellent sedative effect the pulse and arterial tension became normal the BMR was within normal limits and the appetite improved with a gain of 7 kg The thyroid gland however remained abnormal and was hyperplastic with a large uptake of radioactive iodine (93% in 1 hour) No evidence of exophthalmos appeared In the other patient a girl 20 treated with reserpine for 7 months the goiter was of the hyperfunctional type accompanied by exophthalmos and a severe neuropsychic disturbance but no weight loss Improvement on doses of 0 75 mg /day was rapid and after 30 days a maintenance dose of 0 30 mg /day was given for 6 months The patient then was regarded as cured and returned to work 8 months later the excellent result had been maintained Tachycardia disappeared weight was stabilized at 65 kg and diffuse thyroid hyperplasia was no longer perceptible

The 51 patients given combined therapy had various types of hyperthyroidism Treatment consisted of 125 250 mg propyl or benzyl thiouracil and 0 75 1 mg reserpine daily reduced to a maintenance dose of 75 125 mg and 0 20 0 50 mg respectively Immediate results were excellent in 38 patients good in 10 and moderate in 3 Of 29 patients who continued treatment for an average of a year 20 had excellent 5 good and 3 fair results In the 1 patient with poor results hyperthyroidism developed during the menopause and reserpine had to be discontinued because of severe coryza

Studies of Thyroid Function and Peripheral Metabolism of I^{131} Labeled Thyroxin Patients with Treated Graves Disease Recent studies have revealed an abnormality in the peripheral metabolism of thyroxin in patients with active untreated Graves disease In such patients an abnormally large fraction of the extrathyroidal pool of thyroxin is degraded daily

Sidney H Ingbar and Norbert Freinkel[3] studied the distribution and rate of peripheral degradation of exogenous I^{131} labeled thyroxin in 23 patients with Graves disease after restoration of a eumetabolic status Many patients showed persistence of increased fractional rate of turnover of the hormone in peripheral tissues for long periods after induction of symptomatic remission Although induction of thyrotoxicosis medicamentosa by administration of desiccated thyroid or triiodothyronine has been shown to increase the fractional rate of turnover of thyroxin hypermetabolism per se cannot account for the increase noted in patients with treated Graves disease

The thyroid gland could contribute to peripheral degradation of thyroxin by secreting a product that stimulates deiodination or by itself degrading the hormone Analysis of several other factors which might influence peripheral turnover of thyroxin has failed to reveal the cause of the abnormality in these patients

Effect of Reserpine on Hyperthyroidism Attempt at Interpretation and Therapeutic Implications Ch Darnaud Y Denard G Moreau R Voisin and Y Gaichies[4] (Toulouse France) studied the results of short courses of reserpine in 10 patients prolonged administration in 2 and combined treatment in 51

The 10 patients who received short courses (9 30 days) were observed in the hospital and had previously received simple sedation with phenobarbital (100 150 mg /day) The average dosage of reserpine was 1 mg /day divided into 4 doses of 0 25 mg each The drug had a pronounced effect on agitation and neurovegetative dystonia in 7 and a good effect on the other 3 The hypotensive action was manifested secondarily i e the effect on the central nervous system was predominant over that on the peripheral vascular system

(3) J Cl J ve t 37 1603 1614 Nov mber 1958
(4) P sse m d 67 457-460 M r 7 1959

from nerve damage Postoperative recurrence is reported as 2 16% depending on the amount of thyroid tissue removed Radioactive iodine is the treatment of choice in patients with thyroid adenoma presenting a poor operative risk or post operative recurrence It should be considered also in nodular goiter because in the authors experience certain previously expressed objections in regard to its limitations are not com pletely valid

► [I have never been able to understand the frequent comments in the literature to the effect that toxic nodular goiters fail to respond to I^{131} treatment. Certainly our experience agrees with that of Bigg and Merkel and suggests that this is a highly successful method of treatment.—Ed.]

Cardiac Complications in Patients with Nontoxic and Toxic Nodular Goiter and with Graves Disease Beatrice A Berteau William W Engstrom and Norman H Engbring[6] (Marquette Univ) studied 182 patients with toxic and non toxic nodular goiter and 51 patients with Graves disease The distinction between nodular goiter and diffuse hyperplastic goiter of Graves disease appears to be valid clinically path ologically and probably etiologically Patients with toxic nodular goiters usually are elderly and have had the goiter for a long time onset of the hyperthryoid state is usually insidious and overt signs of hypermetabolism are frequently minimal exophthalmos is not present emotional factors sel dom precipitate the disease the peculiar neuromuscular overactivity and the myopathy of Graves disease are not seen adenomas of various ages sizes and degrees of activity are present and the thyrotoxicosis responds less readily to treatment with radioiodine propylthiouracil or excess iodide than the diffusely hyperplastic gland of Graves disease In this series the patients with nodular goiter were much older (average age 65 years) than those with Graves disease (av erage age 38 8 years) Patients with toxic nodular goiter were similar in age to those with nontoxic goiter The only similarity to patients with Graves disease was in the thyro toxicosis

Of the 182 nodular goiters 70 were toxic irregularities of cardiac rhythm (most commonly persistent auricular fibril lation) occurred in 53% of these but in only 24% of those with nontoxic nodular goiter Further of those who had auricular fibrillation chronic or intermittent practically all had demonstrable organic heart disease Therefore if auricu

(6) J Lab & Cl M d 52 687-693 Nov mb 1958

This was the only patient who did not tolerate the drug well

The clinical effects of reserpine in hyperthyroidism of all types cannot be completely explained by the action of the central nervous system nor by a direct antithyroid effect it appears highly probable that there is also an antagonistic effect on thyroid hormone *in the peripheral tissues them selves*

Pharmacodynamic studies indicate that other drugs e g chlorpromazine tetraethylammonium and Regitine® may have an antithyroid effect analogous to that of reserpine thus providing new therapeutic possibilities None of these drugs however have as strong antithyroid properties as *thiouracil* The present study demonstrates that when res erpine is combined with thiouracil the dosage of the latter can be reduced by half with as good or better therapeutic results

► [Similar results have been reported by others (e g Canary and co workers New England J Med 257 435 1957) We have not used reser pine for the treatment of ordinary hyperthyroid patients but have found it most useful in controlling patients who were intensely agitated and showed the picture often referred to as thyroid crisis While there may be some theoretical interest in treating hyperthyroid patients with reserpine it does not appear to have any practical symptomatic advantage over propyl thiouracil for most patients and it leaves the thyroid hyperactivity rela tively uncontrolled In my opinion it should be used only for its sedative action but when used in this way it may be very helpful in severely toxic patients —Ed]

Treatment of Toxic Nodular Goiter with Radioactive Io dine is described by Edward Bigg and James R Merkel[5] Total dosage of I^{131} in the 20 patients (aged *17 75*) varied from 4 to 23 5 mc and the number of doses necessary to com plete therapy varied from 1 to 5 Medication was spaced at intervals of 4 6 weeks

Treatment relieved thyrotoxicosis and all patients showed reduction in the size of the gland sufficient in over half for the gland to be no longer palpable or no longer considered enlarged Though this response was due *in* part to *involution* of hyperplastic areas in the gland parenchyma the authors believe that the nodules themselves responded to the radia *tion* The only complication was myxedema in 1 patient which responded promptly to specific thyroid replacement

Thyroidectomy even in the most capable hands carries a definite mortality rate besides the tragic sequelae of chronic *hypoparathyroidism and laryngeal dysfunction resulting*

(5) Q rt B ll Northwestern U v M School 32 12 14 Fall 1953

from nerve damage Postoperative recurrence is reported as 2 16% depending on the amount of thyroid tissue removed Radioactive iodine is the treatment of choice in patients with thyroid adenoma presenting a poor operative risk or post operative recurrence It should be considered also in nodular goiter because in the authors experience certain previously expressed objections in regard to its limitations are not com pletely valid

► [I have never been able to understand the frequent comments in the literature to the effect that toxic nodular goiters fail to respond to I^{131} treatment Certainly our experience agrees with that of Bigg and Merkel and suggests that this is a highly successful method of treatment—Ed.]

Cardiac Complications in Patients with Nontoxic and Toxic Nodular Goiter and with Graves Disease Beatrice A Berteau William W Engstrom and Norman H Engbring[6] (Marquette Univ) studied 182 patients with toxic and non toxic nodular goiter and 51 patients with Graves disease The distinction between nodular goiter and diffuse hyperplastic goiter of Graves disease appears to be valid clinically path ologically and probably etiologically Patients with toxic nodular goiters usually are elderly and have had the goiter for a long time onset of the hyperthryoid state is usually insidious and overt signs of hypermetabolism are frequently minimal exophthalmos is not present emotional factors sel dom precipitate the disease the peculiar neuromuscular overactivity and the myopathy of Graves disease are not seen adenomas of various ages sizes and degrees of activity are present and the thyrotoxicosis responds less readily to treatment with radioiodine propylthiouracil or excess iodide than the diffusely hyperplastic gland of Graves disease In this series the patients with nodular goiter were much older (average age 65 years) than those with Graves disease (av erage age 38 8 years) Patients with toxic nodular goiter were similar in age to those with nontoxic goiter The only similarity to patients with Graves disease was in the thyro toxicosis

Of the 182 nodular goiters 70 were toxic irregularities of cardiac rhythm (most commonly persistent auricular fibril lation) occurred in 53% of these but in only 24% of those with nontoxic nodular goiter Further of those who had auricular fibrillation chronic or intermittent practically all had demonstrable organic heart disease Therefore if auricu

(6) J Lab & Cl M d 52 687 693 N mb 1958

lar fibrillation is present in an elderly patient with a nodular goiter the chances are almost 100% that independent organic heart disease is present and the odds are 2 to 1 that the goiter is toxic

Cardiac arrhythmias were much less frequent among the patients with Graves disease than in those with toxic nodular goiter occurring in only 6 (12%) of the latter

No difference in the level of circulating thyroid hormone existed between patients with fibrillation and those with sinus rhythm With adequate treatment of the thyrotoxicosis among patients with nodular goiter spontaneous return to sinus rhythm occurred in only 6 of the 25 with arrhythmias Therefore while hyperthyroidism appears to precipitate arrhythmias older age and associated organic heart disease apparently are fundamentally more important in causing their development Improvement or even disappearance of heart failure was the most common favorable effect when hyperthyroidism was controlled

Thyroid Function in Supraventricular Tachycardias Turnover of Intravenously Infused I^{131} Labeled Thyroxin and Red Blood Cell Uptake of I^{131} Labeled 1 Triiodothyronine George S Kurland Arnold Golodetz Milton W Hamolsky and A Stone Freedberg[7] studied thyroid function in 28 euthyroid patients with paroxysmal or recent prolonged atrial fibrillation and in 11 with paroxysmal atrial tachycardia The serum protein bound iodine level basal metabolic rate and thyroidal I^{131} uptake were within normal limits In 11 patients the fate of intravenously administered I^{131} thyroxin was studied The half time of disappearance of plasma radioactivity following infusion of I^{131} labeled thyroxin ranged from 4 1 to 6 8 days and averaged 5 74 days—significantly faster than the turnover in previous studies of euthyroid human subjects The thyroxin distribution space ranged from 8 to 16 4 L (average 12 2 L) in contrast to a range of 7 12 L (average 9 9 L) in the control group The daily degradation rate of thyroxin varied from 52 to 126 μg /day (average 83 6) in the group under study but was only 36-61 μg in the control group The 2 hour in vitro red blood cell uptake of I^{131} triiodothyronine from whole blood in 18 male patients with atrial arrhythmias was 18 6%/100 hematocrit In 8 of these patients the values

(7) J Cl Endocr of 19 9 102 J nua y 1959

were in the range often seen in thyrotoxicosis The red blood cell uptake of I^{131} triiodothyronine in 21 female patients similarly studied averaged 16.5% Seven of the 21 had uptakes greater than 18% the upper limit for euthyroid females Of the 28 patients with atrial fibrillation 12 had abnormal red blood cell uptake Among the 11 with paroxysmal atrial tachycardia the red blood cell uptake was abnormal in 3 Five patients were treated with large doses of potassium iodide although they were considered euthyroid Significant improvement was noted in each

Both turnover rates and changes of the relative plasma tissue affinities for hormones indicated by the red blood cell data suggest increased availability of thyroid hormones to tissues but fail to explain why this increased availability did not result in general hyperthyroidism but affected only the heart A selective sensitivity of the heart to thyroid hormones might be suggested However it is likely that local factors altering myocardial metabolism play a role in addition to neural and *hormonal influences It is thus significant that the* patients with paroxysmal atrial fibrillation were in an age group (40-80 years) in which an underlying substrate of coronary atherosclerosis is likely

Thyrotoxic Myopathy In thyrotoxicosis muscular weakness is usually localized in the proximal muscle groups primarily those of the lower extremities and is manifested by difficulty going up and down stairs and rising from a sitting position Mild muscular weakness is a common symptom whereas advanced weakness including pronounced paresis and atrophy is less frequent

Ragnar Hed Lennart Kirstein and Curt Lundmark[8] (Sodersjukhuset Stockholm) studied 20 thyrotoxic patients All had electromyography and muscle biopsy in addition to the usual clinical examinations Pronounced symptoms of atrophy or muscular weakness were evident in 11 10 of whom (7 women and 3 men) were greatly disabled In 8 the symptoms were only slight or moderate

The clinical signs of thyrotoxicosis in the patients with high grade muscular weakness were only slight thyrotoxic eye symptoms were completely absent As a consequence many of these patients had remained untreated for a number of years In several patients the muscular weakness began

(8) J Neurol Neurosurg & Psychiat 21 270 278 November 1958

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(7) J Clin Endocrin l 19 92 10 January 1959

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(8) Neu os g & P y hiat. 21 70 278 N mbe 1958

some years before definite clinical signs of thyrotoxicosis were observed In all but 1 this weakness was principally localized in the proximal muscle groups primarily those of the lower extremities

Five of the 10 patients with crippling muscular weakness had impaired carbohydrate metabolism of the diabetic type Pathologic spontaneous creatinuria was noted to be present in all 10 patients but no correlation was demonstrated be tween the degree of muscular weakness and the creatinuria



Fg 93 (C t y f H d R t l J N u l N g & P y h t 21 270 78 N v mb 1958)

Signs of myopathy were revealed in all 17 patients under going electromyographic examination of the quadriceps or deltoid muscles One patient showed neuropathic signs as well These findings strengthen the assumption that the muscular weakness in most cases of thyrotoxicosis which is often interpreted as asthenia is caused by true myopathy Probably there is only a difference in degree between thy rotoxicosis with only slight muscular weakness and that with the disabling forms so called chronic thyrotoxic myopathy

The histologic changes in the musculature were generally slight and no pathologic increase in adipose tissue was ob served In only 2 cases were relatively pronounced changes

with necrosis recorded The necrotic regions in one of these presented comparatively abundant inflammatory cells and so called myocytes (Fig 93)

The observations indicate that long standing untreated thyrotoxicosis is probably a significant factor in the development of disabling thyrotoxic myopathy

Onycholysis in Hyperthyroidism is reported by M N Luria and S P Asper Jr[9] (Johns Hopkins Univ) Ony

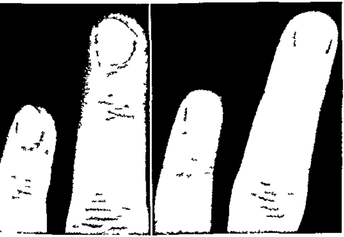


Fig 94 (l ft) —M m l ony h ly f 4th d 5th fi g
Fig 95 (ght) —N mal ppea f l f t eatment
(Co t y f Lu M N d A p S P J An I t M d 49 102 108 J ly 1958)

cholysis in exophthalmic goiter is not unusual Whereas in the healthy nail a distal convexity of the curvilinear junction of the nail from its bed is noted in onycholysis reversal of this curve results from separation of the terminal central part of the nail from the bed Thus beneath the end of the nail an additional free space is left in which debris may collect Uniquely these changes occur most often in the 4th finger As the changes progress they extend to involve the 5th finger and later the other fingers and thumb Onycholysis of the toenails may also occur

Woman 37 presented with nervousness irritability moderate heat intolerance tremor proptosis and blurred vision for 11 months Blood pressure was 120/60 mm Hg and pulse rate 100/minute She showed slight tremor of the hands and bilateral proptosis with edema

(9) A I t M d 49 102 108 J ly 1958

of eyelids and diplopia in all fields of vision the left eye could not be deviated superiorly The thyroid was diffusely enlarged Radioactive tracer test was in the hyperthyroid range The nails showed minimal onycholysis of 4th and 5th fingers (Fig 94) of both hands Normal metabolic rate was achieved in 4 months on treatment with methimazole and the nails appeared normal (Fig 95)

In the authors experience onycholysis has been observed only in hyperthyroid patients with diffuse goiter There seems to be no age or sex predilection Exophthalmos may or may not coexist The condition improves with treatment of hyperthyroidism and usually disappears when the euthyroid state is achieved What role the metabolic and hormonal derangements of hyperthyroidism play in bringing about this curious manifestation is unknown This sign is not pathognomonic of hyperthyroidism since similar changes in the nails have been reported in patients with other systemic diseases such as syphilis hypothyroidism and chronic arthritis and in fur workers and persons with injured nails

Gross Digital Clubbing and Exophthalmic Ophthalmoplegia in Thyroid Disorders were observed by A G Freeman[1] (Univ of Bristol) in a patient with untreated active thyrotoxicosis

Man 54 was hospitalized because of a 6 month history of nervousness irritability palpitations and increasing prominence of the eyes Despite a good appetite weight loss was about 28 lb The eyelids had been puffy for 4 weeks with ocular pain and photophobia for 3 days

On examination the patient was nervous and agitated the skin was warm and moist and a fine tremor of the fingers was present The resting pulse rate was 130 with normal rhythm blood pressure was 180/95 mm Hg The thyroid gland was easily palpable and uniformly enlarged and a loud systolic bruit was audible over the neck Bilateral proptosis (exophthalmometer right eye 25 mm left eye 26 mm) was present Lid lag lid retraction and widening of the palpebral fissures were evident The eyelids were edematous and inflamed and chemosis was present There was some weakness of elevation and abduction in both eyes and the patient had double vision when attempting to look to the extreme left and right Visual acuity of the right eye was 6/6 of the left 6/5 the ocular fundi and visual fields were normal There was no pretibial myxedema but gross clubbing of the fingers and toes was evident (Fig 96) The face showed no signs of acromegaly The skin over the forehead showed some thickening and furrowing The heart lungs and abdomen were clinically normal

Radioactive iodine measurements showed that the total uptake was 82% of the dose at 4 hours and at 48 hours the protein bound I131 level in the plasma was 1 35±0 08% of the dose per liter values consistent with thyrotoxicosis

(1) Lancet 2 57 60 July 12 1958

Bilateral tarsorrhaphy was done followed by treatment with radio active iodine The patient became euthyroid and in 12 months the exophthalmos and ophthalmoplegia showed definite improvement The extreme digital clubbing has remained

It appeared that development of digital clubbing closely followed onset of symptoms and signs of a toxic goiter and progressive exophthalmos The fact that gross digital club

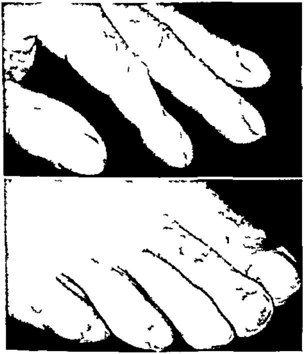


Fig 96 (Court y f F m A G La t 2 57 60 J ly 1 1958)

bing is now reported in association with exophthalmic ophthalmoplegia in hyperthyroidism as well as in induced euthyroid and hypothyroid states adds further support to the view that this syndrome with or without pretibial myxedema is a clinical manifestation of pituitary dysfunction

Metabolic Observations in Case of Thyrotoxicosis with Hypercalcemia are reported by C R Kleeman S Tuttle and S H Bassett[2] (Univ of California Los Angeles)

(2) J Cl E doc 1 18 477 491 M y 1958

Man 56 had progressive anorexia abdominal complaints pruritus heat intolerance progressive weakness increasing pigmentation polyuria and polydipsia for about a year The thyroid was about twice normal size firm and smooth Serum levels of calcium were 11 3 13 6 and of phosphorus 3 9 4 3 mg/100 ml Alkaline phosphatase was 5 2 and 4 7 Bodansky units on 2 occasions Serum protein bound iodine was 17 4 µg thyroid uptake of I^{131} was 63% in 6 hours and 66% in 24 hours The BMR was +23% and +28% There was no x ray evidence of demineralization osteitis fibrosa cystica subperiosteal bone resorption or soft tissue calcification There were no renal calcifications

A 125 day balance study done as the patient became euthyroid showed that the excessive urinary and fecal loss of calcium bore little relation to the diet or to the level of nitrogen balance A high phosphate diet ameliorated the metabolic abnormality and corrected the hypercalcemia Successful treatment of the thyrotoxicosis produced similar changes in calcium metabolism Throughout the study renal excretion of calcium reflected primarily alterations of the underlying osseous metabolism rather than variations in dietary calcium whereas fecal excretion of calcium consistently exceeded dietary intake and was relatively constant regardless of the level of thyroid activity In a second portion of the study a 50 day balance study during recurrence of thyrotoxicosis the metabolic defect in the osseous metabolism was less pronounced Hypercalcemia was not present Urinary calcium excretion increased only slightly over that during a euthyroid period and fecal losses were unchanged

During the study period the patient lost at least 3% of the skeletal calcium without apparent x ray change It is concluded that thyrotoxic bone disease is not noted more often because the underlying disorder is corrected before demineralization proceeds to a clinically demonstrable level

The authors consider the possible causes of hypercalcemia and excessive excretion of calcium with thyrotoxicosis The return to normal during euthyroidism and amelioration after phosphorus administration suggest a direct effect of excessive thyroid hormone on skeletal metabolism with reversal or counteraction of the effect by phosphorus Presence of hypercalcemia in this patient and in the few others described in the literature suggests a defective control on renal clearance of calcium by parathyroid secretion

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Another case was reported in the 1958-59 YEAR BOOK (p 705) by Lpstein *et al* It now appears that hyperthyroidism must be considered in evaluating the cause of hypercalcemia and that hypercalcemia should be sought in patients with hyperthyroidism While the number of patients thus affected may not be very large the rapid development of renal damage and of mental disturbances in such cases puts a high premium on early diagnosis and treatment —Ed.]

Thyroglobulin Antibodies in Multiple Thyroid Diseases are discussed by Robert M Blizzard George J Hamwi Thomas G Skillman and Warren E Wheeler[3] (Ohio State Univ) Autoimmunization to autogenously released thyroglobulin has recently been implicated as a causative factor in Hashimoto s thyroiditis and spontaneous myxedema Circulating thyroglobulin antibodies have been demonstrated in the serum of patients with these diseases and serve as a basis for this hypothesis Animal studies further support this thesis homologous thyroglobulin injection produce antibodies and lymphocytic destruction of thyroid tissue Diseases other than thyroiditis and spontaneous myxedema seemed likely to offer opportunity for extrathyroidal circulation of thyroglobulin and hence antibody formation Accordingly the authors studied subjects with and without thyroid disease determining the prevalence of circulating thyroglobulin antibodies in each group

Two methods were used to demonstrate circulating antibodies The red cell hemagglutination technic described by Boyden and applied by Rose and his associates was slightly modified and used for all serums A second method utilized for many positive serums was the agar gel precipitation technic described by Doniach and Roitt used without modification Penicillin antibodies were tested by measurement of agglutination sensitized red cells with exposure to suspect serum as described by Ley *et al*

Thyroglobulin antibodies demonstrated by the red cell hemagglutination technic were frequently found in thyroid disease Poor correlation existed between the types of disease and the presence of antibodies Since antibodies occur in a large proportion of patients with thyrotoxicosis spontaneous myxedema *nontoxic nodular goiter and chronic thyroiditis* the production of antibodies may be secondary to any hyperplastic stimulus or nonspecific thyroid insult causing thyroglobulin release from the local confines of the thyroid follicle This occurs in many thyroid disorders

(3) New E gla d J Med 60 112 116 J n. 15 1959

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(3) New England J Med. 260 112 116 Jan. 15 1959

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body titers 10 with Hashimoto s disease and 3 with sub acute thyroiditis Antibodies were determined by the tanned cell hemagglutination technic using human group O cells and purified thyroglobulin

The normal appearance of the basement membranes of thyroid follicles was noted in glands from patients without antibodies (Fig 97) The membrane stained intensely and evenly It was 0 1 0 2 µ wide and closely applied to the base of the epithelial cells forming a continuous unbroken lining and completely sealing off the follicle from the capillary vessels Even in hyperplastic papillary processes the basement membrane closely follows the proliferative epithelium

Abnormal basement membranes were noted mainly in thyroid glands from patients with high antibody titer The damage was entirely focal and consisted of fragmentation beading and duplication of the basement membrane The fragmentation appeared as sharp breaks in continuity often associated with a wavy irregular appearance unlike the straight smooth line of the normal membrane Beading was often noted as minute argentophil dots or globules In duplication the membrane is split into two or more layers This was observed more often in subacute thyroiditis than in Hashimoto s disease or thyrotoxicosis The changes in Hashimoto s disease were qualitatively similar to those in thyrotoxicosis but were diffuse and more severe (Fig 98) All 10 patients with Hashimoto s disease had extremely high antibody titers and all showed severe diffuse injury to the basement membrane In subacute thyroiditis the appearance was different There was an increase in reticulin like fibers between the follicles and fragmentation was coarser In follicles showing giant cells or swollen epithelium there was considerable duplication of the membrane whereas intact and normal looking follicles revealed no such change

These findings establish a clear relation between basement membrane damage and presence of antibodies in significant titer It is difficult to believe that these circulating antibodies possess any significant cytotoxic effect because they are present in high titer in some patients with thyroid hyperfunction If a cytotoxic effect were present the result would be suppression of function It seems probable that the antibodies are related to phagocytosis of extravasated colloid and that the primary effect in Hashimoto s disease is tail

and permits further histologic physiologic and functional alterations resulting from the antigen antibody reaction and the subsequent autodestructive process

Autodestructive phenomena in addition to being an etiologic factor in spontaneous myxedema and Hashimoto s thyroiditis probably account for some cases of cretinism and have a role in controlling thyrotoxicosis

Significance of Basement Membrane Changes in Thyroid Disease Thyroid antibodies have been demonstrated in



F g 97 (left) — S ct on of thy d gl nd how g no m l lat b p of ba e m t membra e t p ll v l S l ed ced f m ×650
F g 98 (ght) —S ba me t m mb e d m g n H h t d e Sl r d d f m ×400
(C u te y of Stu rt A E d All W S A Lan t 1204 120(D 6 1958)

Hashimoto s disease and the suggestion made that the stimulus for their production is the slow liberation of colloid from the thyroid follicles Similar antibodies have been described in thyrotoxicosis and subacute thyroiditis It appears that thyroglobulin is immunologically inert when contained within the follicles but is treated by the host as a foreign protein when extravasated into the interstitial tissues

Angus E Stuart and W S A Allan[4] (Univ of Edinburgh) studied thyroid glands from 8 patients with thyrotoxicosis and high antibody titers 10 with thyrotoxicosis but no anti

(4) La c t 2 1 04 1 06 Dec 6 1958

of serum constituents confirmed the defect in hormone production by demonstrating that 98% of the serum radioactivity represented iodinated compounds which migrate more rapidly than proteins

These facts served to identify the difficulty as a disturbance in thyroid biosynthesis connected with oxidation of iodides A similar anomaly has been noted in cretins with goiter (Stanbury type I) and reproduced in a normal person

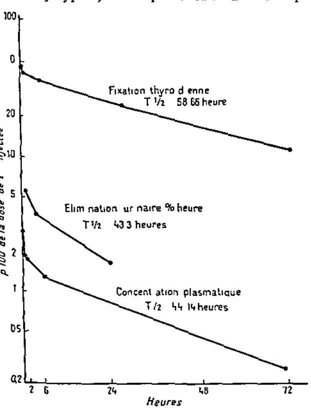


Fig 99—Dec f d t ty th th mp rtm t thy d pl m d (C rte y f D rt J t l A doc 1 19 343 355 M Ap 1958)

treated with methimazole The authors believe that this is the first instance in which it has been recognized in acquired myxedema in an adult who had received no synthetic antithyroid preparation Etiology in this case remained undetermined Treatment of triiodothyronine produced rapid and

ure of the integrity of the basement membrane If the function of the basement membrane is to maintain the immunologic integrity of the follicle by preventing access of colloid to the interstitial tissue a break in the continuity of the membrane as observed in this series would provide an anatomic basis for thyroid antibody formation

► [The presence of autoantibodies to thyroglobulin in patients with Hashimoto s struma was discussed in the 1958 59 YEAR BOOK (p 666) The previous 2 papers show that many other processes can produce similar autoantibodies Since hyperthyroidism is not usually accompanied by the type of progressive inflammatory process which is seen in lymphoid thyroiditis Blizzard s suggestion that an autoimmune process may help control hyperthyroidism spontaneously seems a bit premature Future observation may confirm this hypothesis however if it can be shown that hyperthyroid patients who have circulating autoantibodies are more likely to have a medical remission of their disease than those without autoantibodies

Additional papers dealing with this problem have been published by Belyavin and Trotter (Lancet 1 648 Mar 28 1949) Anderson Goudie and Gray (ibid p 644) and Cline Selenkow and Brooke (New England J Med 260 117 1959)

A good statistical survey of struma lymphomatosa has been published by Woolner McConahey and Beahrs of the Mayo Clinic (J Clin Endocrinol 19 53 1959)

Several interesting case reports showing good therapeutic effects of salicylates in the treatment of acute thyroiditis were presented by Torikai and Kumaoka (New England J Med 259 1265 1958) I have tried this remedy in 2 cases with good results At present it seems best to try aspirin in large doses before turning to somewhat more potent (but more dangerous) drugs such as the corticosteroids —Ed]

Myxedema with Goiter Due to Disturbance of Intrathyroid Hormonogenesis of Late Appearance in Adult is reported by *Jacques Decourt R Fauvert J L de Gennes* and *G Saucier*[5] with the technical collaboration of R Guerin M Th Guerin A Loverdo and R Michel

Man 60 within a few months showed myxedema with a goiter Metabolic study with I^{131} disclosed a disturbance of thyroid hormone production In apparent disagreement with clinical signs the curve of thyroid fixation of radioactive iodine showed a rapid increase to 42% the first hour and then a rapid fall to 11% at 72 hours Precise analysis of different parameters of metabolism of I^{131} showed a unique compartment composed entirely of iodinated compounds not used in manufacture of thyroid hormones These were in free exchange between thyroid and plasma and their radioactive decrease was controlled by renal clearance (Fig 99) Half life for thyroid iodine was 58 hours (it is 30 5 days in normal persons and 10 4 days in hyperthyroid patients) For circulating plasma iodine it was 44 14 and for urinary elimination 43 3 hours Volume of distribution of iodides was 47 6 L or 20 94 L intrathyroid and 26 7 L extrathyroid i e 0 33 L/kg weight

Study of localization of circulating I^{131} in electrophoretic analysis

(5) Ann endocrin 1 19 343 3 5 Ma Ap 1958

of serum constituents confirmed the defect in hormone production by demonstrating that 98% of the serum radioactivity represented iodinated compounds which migrate more rapidly than proteins

These facts served to identify the difficulty as a disturbance in thyroid biosynthesis connected with oxidation of iodides A similar anomaly has been noted in cretins with goiter (Stanbury type I) and reproduced in a normal person

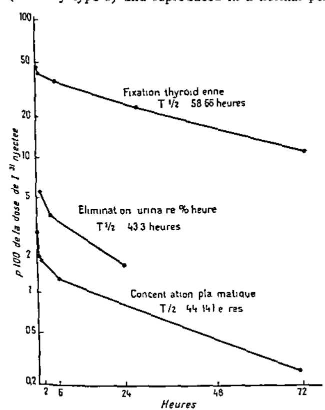


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continuous improvement in all signs of myxedema and regression of the goiter

► [If present theories about the nature of this (hereditary?) defect are correct one would have to suppose that this patient had had a partial defect in hormone synthesis all his life but that he had been able to "keep up" without developing a goiter until some undefined additional influence either further inhibited his thyroid or increased the demand for hormone to such a point that goiter formation was necessary to permit his crippled gland to secrete enough hormone to meet the body's needs —Ed]

Demonstration of I^{131} of Incidence of Lingual Thyroids in Myxedema C Kellershohn and J Martin[6] (Nancy France) report that during 8 months systematic study of 23 patients with myxedema revealed ectopic thyroids in 14 (7 lingual 4 suprahyoid and 3 juxtahyoid) with absence of thyroid tissue in the normal location Six patients had a thyroid in normal position and 3 had no thyroid tissue This study was initiated after finding an ectopic thyroid in a child with acquired myxedema In 7 of the 14 patients with ectopic thyroid a scanning method was used to determine the shape and weight of the thyroid In 6 weight was 1 5 5 Gm (average about 3 Gm) In the other patient a lingual thyroid weighed 8 Gm the only one discovered by mechanical means rather than by radioiodine

In these 14 patients with myxedema and ectopic thyroids thyroid fixation 1 hour after ingestion of I^{131} was 2 12% and at 24 hours 3 23% Fixation the 1st hour was relatively high with respect to that at 24 hours Measurements made several days after ingestion indicated more rapid disappearance of I^{131} than in the normal thyroid This was interpreted as due to hyperfunction of ectopic thyroid tissue and the low level of fixation was attributed to the small volume of thyroid tissue The presence of hyperfunction was confirmed by biopsy in 1 patient It is noteworthy also that the 14 patients with ectopic thyroid tolerated suppression of treatment for 2 months preceding I^{131} examination better than the 3 patients with athyreosis

Recently MacGirr and Hutchison advanced the theory that the principal cause of myxedema is dysgenesis of the thyroid a developmental defect related to more or less incomplete migration of embryonic anlages along the thyroglossal tract with consequent insufficient development due to ectopy and hormonal insufficiency which in turn causes myxedema due

(6) Acta rad 1 51 137 156 F b y 1959

to the small volume of ectopic thyroid tissue Findings of the present study appear to corroborate this hypothesis

Possibly myxedematous patients with lingual thyroids might be treated by autografting of ectopic tissue into an anatomic region which would allow sufficient development to assure hormonal needs

► [A case falling into this group has been reported by Odell and collaborators (J Clin Endocrinol 19 363 1959) In their patient the lingual thyroid regressed rapidly during treatment with 75 μg triiodothyronine —Ed]

Neurologic Manifestations of Myxedema Stewart N Nickel and Boy Frame[7] (Henry Ford Hosp) reviewed data on 100 patients with myxedema and found the nervous system significantly involved Some of the major and initial manifestations are neurologic in origin Cerebral function is markedly altered with symptoms ranging from anxiety and depression to severe schizoid and manic behavior Hallucinations occur involving sight sound taste and smell Organic mental changes are often resistant to average doses of thyroid and as much as 9 gr daily is required by some patients for improvement In all the coma of myxedema occurred only during winter suggesting that environmental cold is a precipitating factor In the past prognosis in coma was poor and in most instances irreversible Availability of rapidly acting thyroid preparations such as l triiodothyronine which returns the metabolic rate to normal within 24 hours may alter prognosis in such patients

Abnormal reflexes in myxedema are striking but the changes are not those usually noted in peripheral neuritis Reflexes in myxedema are usually prompt and active with a delayed relaxation phase In peripheral neuritis reflexes are absent or depressed with no alteration in the contraction or relaxation phase The abnormalities in reflexes are attributed to abnormality in the contractile substance of the individual muscle fibers Subjective sensory complaints in myxedema are prominent but out of proportion to objective findings Subjective weakness is also present but there is little evidence to indicate objective motor deficit Cerebrospinal fluid protein is increased probably constituting another manifestation of the increased capillary permeability in myxedema

One predominant feature of myxedema is the tendency for

(7) Neu l gy 8 511 517 J ly 1958

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(7) N 1 gy 8 511 517 J ly 1958

myxedematous collections to occur in various tissues most commonly about the eyes but also in serous cavities such as the pericardium and pleura Some neurologic signs could result from similar interstitial accumulation in the nervous system or might be secondary to changes in cerebral vascular dynamics Another possible mechanism is interference with function of the enzyme systems Thyroxin may be a coenzyme in the important oxidation reduction pathways Any decrease of thyroid might limit the amount of enzyme available Because important enzymes such as succinoxidase are depressed in the tissue of patients with myxedema and because the nervous system depends on these oxidative enzymes for normal metabolic activity deficiency would interfere with nerve tissue function

Cerebrospinal Fluid Proteins in Myxedema with Special Reference to Electrophoretic Partition were studied by David Bronsky Harold Shrifter J de la Huerga Alvin Dubin and Sheldon S Waldstein[8] (Chicago) in 27 patients Cerebrospinal fluid pressure was between 200 and 270 mm water in 5 patients and between 180 and 200 mm in 5 The fluid was crystal clear and contained the normal numbers of cells The only significant abnormality was elevation of the level of total protein in 25 patients (mean value 98 mg/100 cc) A concentration over 100 mg was noted in 12 patients

In 9 patients electrophoretic partition of cerebrospinal fluid protein showed a significantly greater concentration of gamma globulin than in controls Concentration of gamma globulin in serum was also significantly increased in myxedema The other fractions of both cerebrospinal fluid and serum proteins were normal In both myxedema and control groups pattern of proteins in the cerebrospinal fluid was not significantly different from that in the serum No prealbumin fraction of cerebrospinal fluid proteins was noted in myxedema and this fraction was found in only 1 control

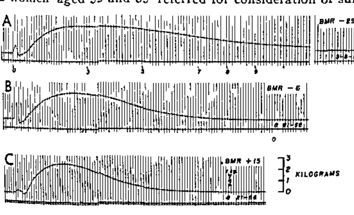
No correlation was noted between degree of elevation of cerebrospinal fluid protein and clinical status of the patient Presence of myxedema did not affect development of cerebrospinal fluid changes characteristic of other diseases

Severe Uterine Bleeding and Degenerative Skeletal Muscle Changes in Unrecognized Myxedema Disturbances in

(8) J Clin E docrinol 18 470 476 May 1958

thyroidal function in premenopausal women are often associated with abnormalities of menstruation Menorrhagia or amenorrhea may develop in patients with spontaneous or postoperative myxedema When amenorrhea occurs in a premenopausal woman with myxedema diagnosis of hypopituitarism with secondary hypothyroidism should be considered and excluded

Griff T Ross Donald A Scholz Edward H Lambert and Joseph E Geraci[9] (Mayo Clinic and Found) observed 2 women aged 55 and 35 referred for consideration of surgical treatment for intractable profuse uterine bleeding



Fg 100 —R d f a kl j k (A h ll t d fl) *A* bef d *B* d C d g t tm t f myx d ma t al l 0 01 sec d t rv ls I t l d flection d f m la c t t p d d by t p A h ll tend wh h m t t fl (Courtesy f R G T *t l* J Cl n Endoc n l 18 492 500 M y 1958)

gical treatment for intractable profuse uterine bleeding Severe menorrhagia lasting 6 10 days was present during the 6 months preceding hospitalization in the first patient After 5 days of oral treatment with desiccated thyroid uterine bleeding ceased The menstrual pattern subsequently returned to normal periodicity and flow

In the second patient myxedema in all probability began after the last pregnancy Nothing suggested anterior pituitary insufficiency since lactation and cyclic menstrual periods were re established following parturition Exsanguination was extreme on hospitalization The uterine bleeding stopped after 7 days of desiccated thyroid therapy After 3 months of treatment the patient was clinically euthyroid

(9) J Cl E docri l 18 49 500 M y 1958

the facies showed remarkable change and menses were normal

Pretreatment electromyographic examination of the calf anterior tibial biceps brachii 1st dorsal interosseous and sacrospinal muscles in the second patient did not reveal spontaneous fibrillation of the type seen in denervated muscle nor demonstrate fasciculation but it did reveal in some areas abnormal irritability of muscle fibers to mechanical stimulation with the needle electrode Movement of the electrode particularly in the calf and sacrospinal muscles occasionally evoked trains of positive waves This was less evident in an electromyographic examination made 3 months after treatment was begun

The abnormal irritability of the muscle, although minimal in degree in some respects resembled that associated with degeneration of muscle fibers in thyroidectomized rabbits The mechanical twitch of the adductor pollicis muscle in response to a single stimulus applied to the ulnar nerve was prolonged before treatment and became shorter with administration of desiccated thyroid Similarly in measurements of speed of contraction and relaxation of the calf muscle in the Achilles tendon reflex the mechanical response before therapy was greatly prolonged particularly in the relaxation phase but returned to normal range as treatment became effective (Fig 100)

► [Additional discussion of abnormal smooth muscle function in hypothyroidism are found in papers by Maggiolo and co-workers (Ann endocrinol 19 968 1958) and Mussio Fournier (Presse med. 66 711 1958) The former discusses changes in the gallbladder urinary bladder and uterus the latter is concerned with colonic function —Ed]

Comparison of Metabolic Effects of Different Thyroid Preparations Rapid onset of increased nitrogen excretion after daily administration of desiccated thyroid and diminution of the catabolic effect immediately on cessation of therapy appeared inconsistent with the concept that this preparation is slow to act and prolonged in effect Consequently the effects of single large physiologically comparable doses of triiodothyronine thyroxin and desiccated thyroid were studied in 6 myxedematous and in 2 euthyroid patients

Laurence H Kyle John J Canary Richard J Meyer and Frances P Pac[1] (Georgetown Univ) report that all three

(1) J Clin Endocrinol 18 950 965 September 1958

preparations are similar with regard to rapidity and duration of action as judged by such indexes of metabolic acceleration as nitrogen excretion BMR serum cholesterol level and pulse rate In the patients with myxedema identical clinical responses followed treatment with triiodothyronine and desiccated thyroid The differences in response as determined by the various indexes of metabolic acceleration were more pronounced between the subjects than between the compounds Triiodothyronine induced minimal rise in the serum protein bound iodine level whereas desiccated thyroid induced a rise that was more consistent with other indexes of metabolic acceleration The calorigenic activity of desiccated thyroid may depend on its content of or rapid conversion to triiodothyronine and thyroxin

Recent emphasis on the potency of triiodothyronine has engendered the belief that its effects are strikingly different from those of desiccated thyroid and has encouraged the notion that it is a more effective therapeutic agent The similarities between various thyroid compounds deserve equal stress

Thyroid Function of Euthyroid Patients during and after Treatment with Triiodothyronine was studied by Clayton Rich[2] (Rockefeller Inst) Evaluation of thyroid function shortly after treatment of patients with triiodothyronine is complicated because of changes brought about by the drug itself These include increased metabolic rate and depression of both thyroidal I^{131} uptake and serum protein bound iodine concentration (PBI) Therefore the state of the inherent thyroid function of the patient can be studied only after triiodothyronine has been withheld for a suitable period

The thyroid function of normal persons was studied after 4 weeks of treatment with 0 15 0 2 mg triiodothyronine/day Each person showed an immediate phase of thyroidal rebound hyperactivity during which the I^{131} uptake was more complete than normal followed in the 3d and 4th weeks after triiodothyronine was discontinued by gradual return of normal function

Rebound increased I^{131} uptake has been observed infrequently during or after treatment with thyroxin and during recovery from thyroiditis However rebound thyroidal hyperactivity of the degree and frequency observed in patients

(2) J Cl E doc I 18 10 4-10 8 S pt mbe 1958

treated with triiodothyronine has been produced otherwise only by administration of goitrogenic drugs such as methimazole During such treatment pituitary release of thyrotropin is stimulated and the thyroid becomes hyperplastic Rebound occurs immediately after treatment because synthesis of organic iodide is no longer inhibited During administration of triiodothyronine its localization in the hypothalamus presumably results in the depression of the pituitary output of thyrotropin The concentration of thyroxin in the serum falls to low levels so when triiodothyronine is discontinued the extrathyroidal organic iodide space is rapidly depleted and acute stimulation of the pituitary results

It appears that several parameters of thyroid function may be affected for about 3 weeks after discontinuation of treatment with triiodothyronine

► [These papers show that triiodothyronine has no special virtues in the treatment of myxedema but may have serious disadvantages since it alters the blood iodine and thyroid radioiodine tests so that they are no longer useful I do not believe that triiodothyronine should be used for the treatment of hypothyroidism except in rare cases (for example in a patient with coronary sclerosis) when the danger of overdosage with thyroid substance makes it desirable to use a preparation whose effects will disappear rapidly after it is withdrawn Even here the preferred preparation for long term treatment is desiccated thyroid —Ed]

Carcinoma of Thyroid in Children after X ray Therapy in Early Childhood is discussed by Donald R Rooney and R Waldo Powell[3] (Emory Univ) Carcinoma of the thyroid in children is being diagnosed with increasing frequency Several explanations have been offered First some of these tumors may have gone unrecognized and untreated in the past and possibly the patients involved reached adulthood before the condition was diagnosed Perhaps some cases are being diagnosed earlier today since patients and physicians have been made more aware of the dangers of neglecting a persistently enlarged nodule Though this possibility may explain some cases in older children it would not seem to account for the over all growing incidence in recent years A second possibility is that an enlarged thymus in infants is in some manner related to the subsequent development of thyroid cancer This too would not seem likely since the so called enlarged thymus in infancy is rather common and the occurrence of thyroid cancer during childhood is uncommon A third possibility to be considered is that the wide

(3) J A M A 169 14 Jan 3 1959

spread use of x ray therapy in infancy during the same period when the rate of thyroid cancer in children was growing is in some manner related to the subsequent thyroid neoplasia

The authors add 10 cases of carcinoma of the thyroid in children aged 17 years or younger to the recorded cases bringing the total to at least 357 These 10 children represent all the cases in this age group recorded in the 6 major hospitals of Atlanta Ga Seven of the 10 received previous x ray therapy in infancy or in early childhood for benign conditions Addition of these 7 to the previously reported thyroid cancers in children after irradiations brings the total to 121 or about one third of all cases reported in children

The fact that the diagnosis of carcinoma of the thyroid in children is increasing correlates among other things with the formerly prevalent use of x ray therapy for benign conditions in early childhood This correlation suggests that irradiation to the head neck or chest in infancy or early childhood may be a causative factor in development of thyroid cancer later in childhood If the correlation is valid there should be in future years a decrease in the incidence of this neoplasm in children as the practice of using irradiation for benign childhood conditions decreases or ceases

► [Others have also reported this unfortunate coincidence (Duffy and Fitzgerald J Clin Endocrinol 10 1296 1950 Clark J A M A 159 1007 1955 Rabinowitz and Katz South African M J 32 723 1958 and Goolden Brit M J 2 954 1958 to mention a few) It seems likely that there is a true causal relationship between irradiation and thyroid cancer in children but no completely satisfactory statistical study has been done Although the incidence of previous irradiation in groups of children developing cancer is high the incidence of cancer among large groups of children previously irradiated has not been determined Despite this it appears wise to avoid irradiation (including I^{131} irradiation) of the thyroid area in children —Ed]

Acute Granulocytic Leukemia after Radioactive Iodine Therapy for Hyperthyroidism In the case reported by William M Kennedy and Robert G Fish[4] (Oteen N C) acute granulocytic leukemia occurred 22½ months after therapy A similar latency period was found in the 5 previously reported cases ranging from 18 to 30 months In these 5 cases the disease was considered to be granulocytic in 3 lymphoblastic in 1 and monocytic in 1

Man 38 had a 10 year history of intermittent weakness nervousness palpitation and occasional exertional dyspnea He had physical

(4) N w E gla d J M d 260 76 77 J 8 1959

signs of hyperthyroidism confirmed by a high protein bound iodine and uptake of radioiodine which did not respond to triiodothyronine daily for 7 days Complete blood count and bone marrow studies were negative He was given 5 5 mc I^{131} and 2 months later was considered euthyroid Repeat blood studies were negative at that time Just 22½ months after taking the therapeutic radioiodine he had sudden left upper quadrant pain He had bilateral retinal hemorrhages scattered purpuric lesions moderate splenomegaly slight hepatomegaly and small lymph nodes The white cell count was 631 000 with 63% unclassified immature cells Platelet and red blood cell count were reduced Sternal marrow examination revealed granulocytic leukemia Despite therapy his condition rapidly deteriorated and he died of a massive cerebral hemorrhage 10 weeks after onset of symptoms Autopsy confirmed the clinical findings

It had been assumed that the frequency of acute leukemia associated with I^{131} therapy for hyperthyroidism corresponded to the expected spontaneous occurrence in the general population Now that 6 cases have been reported it is unlikely that this is purely chance

► [Here the association between irradiation and neoplasm is much less secure Leukemia is a much more common disease than thyroid cancer and the development of leukemia in patients given I^{131} has not been common In a letter to the editor of the New England Journal of Medicine Dr Martin discusses this fallacy and reports a recent case of acute leukemia following subtotal thyroidectomy! (New England J Med 260 941 1959) In reporting another such coincidence Coliez (J radiol et électrol 40 76 1959) concludes that at present there is no proof of causal relationship between radioactive iodine and leukemia Moreover in Coliez case (and in most others in the literature) the doses of radioiodine were very much larger than those used for treatment of hyperthyroidism —Ed]

Papillary Cancer of Thyroid Review of 25 Years of Experience is presented by Edgar L Frazell and Frank W Foote Jr [5] (Mem l Center for Cancer New York) From 1930 to 1954 725 patients with carcinoma of the thyroid were seen 393 (54 2%) papillary tumors were studied

Signs of advanced disease at the primary site such as invasion of pharynx larynx or trachea were not uncommon Such signs of late thyroid cancer were not significantly more frequent in previously treated than in untreated patients Tracheal deviation by the tumor was not an outstanding finding except in bulky lesions Vocal cord palsy was noted on hospitalization in about 8% of all patients Aspiration biopsy of thyroid nodules has been largely discontinued at the Memorial Center not from fear of cancer dissemination but because of evidence that frozen section diagnosis is more trustworthy

(5) Cancer 11 895 92 Sept Oct 1958

Although it is reasonably certain that sharp dissection does not remove all tumor cells this procedure is not incompatible with prolonged asymptomatic survival in some patients Thirteen patients with nonresectable disease in the previously untreated group lived 5 years or over though some of them ultimately died of the effects of the tumors A few have lived over 20 years and at least 1 is clinically cured

It has been widely assumed that a thyroid with a solitary nodule is more likely to be cancerous than a gland with multiple nodules Estimates vary as high as 3 1 in favor of the solitary nodule being cancerous However the impression of a solitary thyroid nodule is a clinical one and not a pathologic diagnosis and a solitary nodule often proves to be a discrete mass in a histologically multinodular gland Although there is limited laboratory evidence that thyroid cancer originates from benign thyroid lesions the authors found numerous examples of benign adenomas and involutional nodules in close proximity to papillary cancer It is suggested that the presence of a solitary nodule may be of limited diagnostic significance

Patients with papillary thyroid cancer are likely to live longer than the customary periods of follow up regardless of the treatment used Arguments based on small numbers of patients with minimal follow up are not convincing of the necessity for or futility of a specific operation for thyroid cancer When irradiation was given as an adjunct to surgery the clinical setting was invariably unfavorable because most of these patients had nonresectable disease Nevertheless a number of long term survivors were observed Complications of irradiation were often severe and in a few instances resulted in death It seems reasonable to believe that irradiation was the deciding factor in the long term survival of some patients

Of 244 determinate patients 126 came under observation before age 40 and 118 were aged 40 or over The 5 year survivals in these 2 groups were 96 8 and 61% However since reactivation of papillary thyroid cancer may not become apparent until long after customary periods of observation it is clear that 5 year survival figures are of limited value in assaying the disease A number of patients living with disease at the end of 5 years have since died of the disease

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(5) Can r 11 895 9 S pt Oct 1958

Thyroid to Anaplastic Carcinoma after Treatment with Radioiodine is described by George Crile Jr and Donald H Wilson (Cleveland Clinic) In experimental animals stimulation of *target organs* by *trophic hormones* causes first hyperplasia then nodular change then cancers that depend for growth on the persistence of the imbalance that caused them and finally development of undifferentiated cancers that are autonomous and unresponsive to endocrine control Present evidence suggests that many differentiated cancers of the thyroid in man are endocrine dependent A total of 13 cases have previously been reported in which growth of such cancers has been increased by treatment which induces hypothyroidism and increases the output of thyroid stimulating hormone (TSH) and just as in animals prolonged stimulation by TSH may convert a low grade differentiated endocrine dependent tumor to a highly malignant anaplastic cancer no longer dependent on TSH

Woman 50 had a proved papillary carcinoma of the thyroid for 34 years with known metastases in the cervical lymph nodes and in the chest for 28 years She had nodules in the thyroid gland and lateral cervical region and diffuse nodular lesions in the base of both lungs Tracer studies showed that the metastases were concentrating I^{131} She received 210 mc I^{131} in divided doses of 30 mc each Sixteen months later the metastases had regressed the basal metabolic rate fell to −33% and clinically she had myxedema She was started on thyroid therapy By 29 months x rays of the chest showed no trace of the metastatic lesions in the lungs At 35 months from the last treatment with I^{131} a rapidly growing mass appeared in the right supraclavicular region which proved to be a highly anaplastic and undifferentiated carcinoma with no resemblance to the tissue of the original biopsy Cobalt-60 teletherapy had no apparent effect She died 39 years after the first nodule was noticed and 5 months after the appearance of the undifferentiated carcinoma

It seems likely that the change from a differentiated papillary carcinoma to an undifferentiated autonomous cancer occurred during the time of exposure to an excess of TSH while the patient was myxedematous To avoid such changes patients with inoperable differentiated thyroid cancers should be given a trial of treatment by feeding desiccated thyroid before treatment with I^{131} or roentgen therapy Operable papillary carcinomas should be removed even if they are not growing since it seems possible for some of them to undergo change to a more malignant type

► [The only question about this case is whether the rapidly growing ana

(7) S g Gynec & Ob t 108 357 360 M h 1959

Treatment of Cancer of Thyroid Postoperatively with Suppressive Thyroid Medication, Radioactive Iodine and Thyroid Stimulating Hormone B Catz D W Petit H Schwartz F Davis C McCammon and P Starr[6] (Univ of Southern California) studied 44 patients with cancer of the thyroid After all available thyroid tissue was removed by surgery patients received 10 units of pituitary thyroid stimulating hormone intramuscularly for 5 7 days followed by 1 2 mc I^{131} as a tracer dose Total body neck and chest were scanned If residual thyroid tissue was suspected a therapeutic dose of I^{131} (40 100 mc) was given Seven days later scanning was repeated Immediately after completion of initial iodine studies desiccated thyroid or sodium levo thyroxin was started the dose being gradually increased until the patient was euthyroid

Remnant tissue was detected in the neck in 96% of the patients after surgery even those with total thyroidectomies To eliminate the thyroid tissue completely surgery should be followed by I^{131} administration after TSH stimulation A scintigram is a more accurate technical device for detecting functional tissue than is the 24 hour I^{131} uptake or the 72 hour urinary excretion study

The 26 patients who were free from metastases survived for periods ranging from 2 to 13 years after diagnosis In the 18 patients with metastases 56% survived and in 4 patients the metastases had ceased to be functional at the time of death An added histologic type at variance with the original cancer was found at autopsy

By administering thyroid hormone early in the course of thyroid cancer in adequately high doses production of TSH by the pituitary will be blocked rate of tumor growth will be reduced and the tumor may maintain itself as a well differentiated type able to respond whenever stimulated for a short period with exogenous TSH and thus able to collect destructive amounts of I^{131} when given after exogenous TSH

Results thus far are promising but a longer follow up will be necessary to ascertain the value of such a regimen

► [This paper is a progress report on the program of treatment described previously (1954 55 YEAR BOOK p 606) It still seems reasonable to me and appears to be working out well in the authors hands —Ed.]

Transformation of Low Grade Papillary Carcinoma of

(6) Cancer 12 371 383 M Ap 1959

Thyroid to Anaplastic Carcinoma after Treatment with Radioiodine is described by George Crile Jr and Donald H Wilson (Cleveland Clinic) In experimental animals stimulation of target organs by trophic hormones causes first hyperplasia then nodular change then cancers that depend for growth on the persistence of the imbalance that caused them and finally development of undifferentiated cancers that are autonomous and unresponsive to endocrine control Present evidence suggests that many differentiated cancers of the thyroid in man are endocrine dependent A total of 13 cases have previously been reported in which growth of such cancers has been increased by treatment which induces hypothyroidism and increases the output of thyroid stimulating hormone (TSH) and just as in animals prolonged stimulation by TSH may convert a low grade differentiated endocrine dependent tumor to a highly malignant anaplastic cancer no longer dependent on TSH

Woman 50 had a proved papillary carcinoma of the thyroid for 34 years with known metastases in the cervical lymph nodes and in the chest for 28 years She had nodules in the thyroid gland and lateral cervical region and diffuse nodular lesions in the base of both lungs Tracer studies showed that the metastases were concentrating I^{131} She received 210 mc I^{131} in divided doses of 30 mc each Sixteen months later the metastases had regressed the basal metabolic rate fell to −33% and clinically she had myxedema She was started on thyroid therapy By 29 months x rays of the chest showed no trace of the metastatic lesions in the lungs At 35 months from the last treatment with I^{131} a rapidly growing mass appeared in the right supraclavicular region which proved to be a highly anaplastic and undifferentiated carcinoma with no resemblance to the tissue of the original biopsy Cobalt-60 teletherapy had no apparent effect She died 39 years after the first nodule was noticed and 5 months after the appearance of the undifferentiated carcinoma

It seems likely that the change from a differentiated papillary carcinoma to an undifferentiated autonomous cancer occurred during the time of exposure to an excess of TSH while the patient was myxedematous To avoid such changes patients with inoperable differentiated thyroid cancers should be given a trial of treatment by feeding desiccated thyroid before treatment with I^{131} or roentgen therapy Operable papillary carcinomas should be removed even if they are not growing since it seems possible for some of them to undergo change to a more malignant type.

► [The only question about this case is whether the rapidly growing ana

(7) & Obst 108 357 360 M h 19 9

plastic tumor was of thyroid origin Other reports somewhat similar in implication to this one have been made by Adams (Australasian Ann. Med 7 306 1958) and Smithers (J Fac Radiol 10 3 1959) who reviewed 6 reported cases responding to desiccated thyroid by prolonged regression of their metastatic thyroid tumors—Ed.]

CARBOHYDRATE METABOLISM

Studies on Relationship between Glucose Oxidation and Intermediary Metabolism I Influence of Glycolysis on Synthesis of Cholesterol and Fatty Acid in Normal Liver was studied by Marvin D Siperstein and Violet M Fagan[8] (Southwestern Med School) in a cell free preparation of normal rat liver

It has been demonstrated that contrary to older concepts glucose can be broken down in the liver by either of two

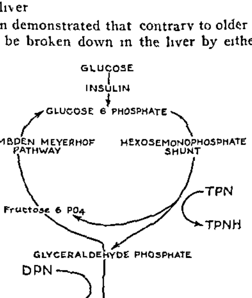


Fig 101—Route of hepatic glycoly (Courtesy of S p te n M D d F g V M J Cl n I st 37 1185 1195 Augu t 1958)

pathways (Fig 101) One is the Embden Meyerhof route over which most of the glucose of the liver cell is probably oxidized the other is the hexosemonophosphate shunt The

(8) J Cl n I t 37 1185 1195 A gu t 1958

quantitative importance of hexosemonophosphate glycolysis is still uncertain Some studies have indicated that this pathway may account for 30 50% of hepatic glycolysis whereas in other experiments the hexosemonophosphate route has apparently been responsible for under 10% of the glucose metabolized by the liver Though the hexosemonophosphate shunt may play a quantitatively minor role in glucose oxidation it seemed possible that it might exert an influence on the regulation of lipid synthesis out of proportion to its function in glucose metabolism

The authors found that the stimulatory effect of glycolysis on these syntheses is primarily due to that portion of glucose oxidation which proceeds via the hexosemonophosphate shunt There is evidence that it is the reduced triphosphopyridine nucleotide generated by the hexosemonophosphate pathway that mediates this effect of glycolysis on fatty acid and cholesterol synthesis When glucose is being oxidized at a rapid rate it appears that synthesis of cholesterol may be regulated by the amount of glucose using each glycolytic pathway oxidation via the hexosemonophosphate route stimulating and that via the Embden Meyerhof pathway depressing sterol synthesis

The process of glucose catabolism by donating protons to specific sites in intermediary metabolism may serve the primary function of regulating certain synthetic processes of the cell

► [This is one of a series of papers concerned with the implications of glucose metabolism as a regulator of anabolic processes The relationship of glucose oxidation to protein synthesis is discussed by Wilson and Siperstein (J Clin Invest 38 317 1959) The subject was reviewed by Wolfe (A M A Arch Int Med 102 493 1958) —Ed]

Studies on Ketone Metabolism in Man II Effect of Glucose Insulin Cortisone and Hypoglycemia on Splanchnic Ketone Production is reported by Harry T McPherson Emile E Werk Jr Jack D Myers and Frank L Engel[9] (Duke Univ) The authors previously described a technic that utilizes hepatic venous catheterization for estimation of net splanchnic ketone body production In subjects without metabolic abnormality a small but significant endogenous net splanchnic ketone body production was detected in the postabsorptive state and on intravenous administration of a ketone body precursor sodium octanoate the ketone body

(9) J Cl I t 37 1379 1393 O t be 1958

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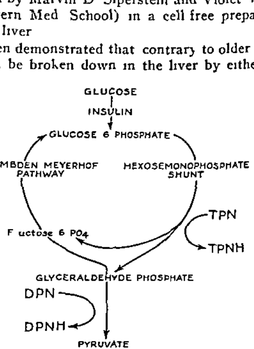


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(8) J Cl I t. 37 1185 1195 Aug t 19 8

are prepared by adding 0 5 ml of 50% sulfosalicylic acid The tubes (blood Clinitest® tubes) are fitted with rubber stoppers and kept available on the ward for blood sugar estimation

In performing the test 4 5 ml freshly drawn venous blood is added to the tube directly from the syringe bringing the total amount of fluid blood and sulfosalicylic acid up to the etched line The tube is stoppered gently inverted three or four times in rapid sequence and vigorously shaken until no trace of red color remains Protein precipitation is complete when the contents are a dull brown this change takes 1 2 minutes of vigorous shaking The tube is unstoppered and centrifuged for 10 15 minutes Exactly 6 drops of water are added to a clean test tube with care to add the drops vertically so that none of the water runs down the side of the tube To the 6 drops of water are added 9 drops of the protein free supernatant A Clinitest® tablet is added to the mixture and the tube is gently agitated while boiling is taking place After a minute or longer the color is compared with the standard Clinitest® urine color chart Correlations of color changes with total content of reducing substances/100 cc blood were trace 125 mg 1+ 125 225 mg 2+ 225-465 mg 3+ 465 585 mg and 4+ 585 mg or more

Occasionally it may be desirable to subdivide the rather wide 2+ range by adding 5 drops of supernatant to 10 drops of water and repeating the test With this modification the following color correlations are found 1+ 225 325 mg /100 cc 2+ 325-465 mg

The sugar content of a series of blood specimens from diabetic patients was determined by the method described and by the hospital clinical laboratory with the method of Kingsley and Reinhold Blood sugar values varied from 34 to 672 mg /100 cc and a reasonably close correlation with the blood Clinitest® predictions based on water standards was noted

Comparison of Response to Intravenously Administered Sodium Tolbutamide in Mild Diabetic and Nondiabetic Subjects The hypoglycemic response of patients with moderately severe diabetes to orally administered tolbutamide has been shown to differ strikingly from that of nondiabetic subjects Indirect evidence of a correlation between tolbutamide response and pancreatic insulin content coupled with experimental support for the view that the drug stimulates endogenous secretion of insulin suggests that this difference may be of more than empiric interest

Roger H Unger and Leonard L Madison[2] (Dallas) injected intravenous sodium tolbutamide into 100 nondiabetic and 79 mild stable diabetic subjects and determined blood glucose concentration a 20-minute intervals for up to

(2) J Cl I t 37 6 7 630 M y 1958

production was increased fivefold This technic was applied to the study of the effects of glucose insulin cortisone and hypoglycemia on ketone body production in man

The addition of glucose or glucose with insulin to the octanoate infusion significantly lowered the net rise in ketone body production noted with octanoate alone Brisk but brief insulin hypoglycemia was induced in 6 subjects by rapid intravenous injection of 0 1 unit of glucagon free insulin/kg body weight This produced definite hypoglycemia about 30 minutes in duration in all subjects the mean lowest blood sugar for the group being 31 0±2 46 mg /100 ml

At the time of study by hepatic venous catheterization 3 hours later the femoral arterial blood glucose levels and the net splanchnic glucose production had returned to normal control levels but the change in ketone metabolism was striking There were significant increases in the arterial and hepatic venous blood ketone levels and a widening of the differences Mean control period net splanchnic ketone body production was 4 7 times greater than that in a previous series If it could be assumed that most new ketone bodies produced in the posthypoglycemic state arose from endogenous fatty acids this might yield a rough estimate of the equivalent quantity of fatty acids being converted to ketones in this state Pretreatment with cortisone failed to suppress the rise in peripheral blood ketone levels and net splanchnic ketone body production occurring in the posthypoglycemic state

In analyzing the results it must be kept in mind that net splanchnic ketone body production was estimated Although the viscera and mesentery drained by the portal vein are not the sources of ketone bodies per se the mesenteric adipose tissue unquestionably contributes ketone body precursors as nonesterified fatty acids to the liver Thus changes in net splanchnic ketone body production may be determined by alterations in adipose tissue fatty acid release and true hepatic ketogenesis

Rapid Estimation of Blood Sugar Content New Method Using Clinitest® Tablets is presented by A S Schneider C R Kleeman and G L Smith[1] (VA Hosp Los Angeles)

METHOD —Test tubes etched with a line at the 5 ml level identical with those in common use for determination of prothrombin time

(1) C l for Med 89 121 12 A g t 1958

Experimental evidence however has shown that tolbutamide potentiates the action of exogenous insulin in totally depancreatized animals The authors results can also be explained on the basis of potentiation by tolbutamide of independently secreted endogenous insulin

Validation of either of these theories of sulfonylurea action would provide a rational basis for the observed differences in tolbutamide response In this event the intravenous tolbutamide response test would constitute an index of beta cell function which might prove useful as a new parameter for the diagnosis of mild diabetes

► [The idea that tolbutamide can be used to evaluate beta cell reserve is ingenious but may be too simple As the authors point out other theories of the mechanism of action of this substance have not been completely discarded —Ed]

Symptoms and Clinical Aspects of Diabetes Mellitus were studied by A G Freeman[3] (Bristol Royal Infirm) in 181 females and 119 males aged 3 85 who attended a diabetic clinic Peak age at onset was in the 7th decade in women and in the 6th in men Ketonuria was noted in 43% Severe diabetic ketosis or coma was present in 25 new patients and in only 5 was the condition not recognized before hospitalization In 4% symptomless glycosuria of diabetic origin was an incidental finding In 5 patients the symptoms appeared suddenly within 24 hours

Woman 63 spent an August afternoon sitting in the sun by the sea On the way home she became sick in the bus and on arrival she complained of severe headache thirst and frequency Within 48 hours she was in coma (blood sugar level 612 mg /100 ml)

One or another of the 5 classic symptoms—polyuria polydipsia polyphagia loss of strength and loss of weight—could be elicited in 95% of the patients yet as a group they occurred in less than 19% Visual disturbances were the presenting symptom in 6% 45% of the patients showed impairment of vision before diagnosis and this was recorded in 49% of the group with ketosis and 42% of the group without ketosis Sudden change from an excessive appetite to anorexia was of considerable diagnostic significance being an almost constant manifestation of impending severe ketosis or diabetic coma Peripheral pain was the presenting symptom in 1% Per onality changes occurred in 5% of the patients before diagnosis and was the presenting symptom in 2 patients

(3) B t. M J 1 1149 1154 M y 17 1958

2 hours thereafter The blood glucose levels of the nondia betics fell rapidly reaching a nadir between 20 and 40 min utes after injection whereas the levels of diabetics includ ing those with a normal or near normal fasting blood glucose value exhibited a more gradual decline (Fig 102)

The results concur with the concept that tolbutamide en hances the release of insulin from the beta cells The resem blance between the nondiabetic tolbutamide response curve

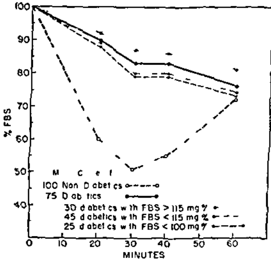


Fig 102 —M an tolbut m de sponse rves f 75 d bet ject Curv f 45 w th f t ng blood sp m n und r 115 mg /100 ml ; l d s 25 w th f st ng blood spec men d r 100 mg /100 ml wh e m c rve l o h wn ep rately (C u te y of Ung R H nd M d L L J Cl n I e t 37 627 630 M y 1958)

and the normal insulin tolerance curve is compatible with a release of stored insulin from the beta cells If this were the case the more gradual hypoglycemic response to tolbuta mide exhibited by diabetic subjects could be ascribed either to diminished insulin stores or to a decreased rate of insulin release in response to betacytotropic stimulation although extrapancreatic interference with insulin degradation is also possible The apparent inverse correlation between the rate of hypoglycemic response and the fasting blood glucose con centration noted in the diabetic group (Fig 102) may be a quantitative expression of the severity of the disease or merely a nonspecific function of the pretest blood glucose level

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(3)—Brit M J 1 1149 1154 May 17 1958

Diabetes in New England Town III Comprehensive Baseline Study in Oxford Mass In 1946 a survey in this community indicated a diabetes prevalence of 1 7% This suggested the estimate of 1 000 000 known and 1 000 000 unknown cases of diabetes in the United States A follow up study in 1950 revealed that persons with a little sugar in the urine or blood sugar levels a little higher than normal developed diabetes eight times oftener than those with normal blood levels (14 4% compared with 1 8%)

Hugh L C Wilkerson Leo P Krall and Frank K Butler[4] (Boston) selected 525 persons from the original 1946 study for long term follow up beginning in 1953 In the original group there were 294 classified as normal 70 as diabetic and 161 as suspect because of postprandial hyperglycemia A total of 307 subjects remained available for study in 1953 Diabetes was diagnosed if the 1 2 hour postprandial venous blood sugar was more than 169 mg /100 ml with glycosuria The blood sugar suspect group had levels between 140 and 169 mg and the normal group levels under 140 mg /100 ml The suspect and normal groups were combined and designated as nondiabetic numbering 235 and 72 were considered diabetic

Despite the attrition of time and migration the group with diabetes increases as persons in the blood sugar suspect group develop diabetes eight times faster than the normal control group Comprehensive physical examinations show that abnormalities are significantly more frequent in the diabetic group in comparison to the nondiabetic group particularly in the eyes heart and great vessels In contrast to the usual reports in the literature this study showed that males are just as likely to have diabetes mellitus as females and that while most known diabetics are past middle age the condition is found in all age groups The person with diabetes has three times as many relatives with diabetes as the nondiabetic About two thirds of patients with diabetes have one or more known relatives with diabetes

The family physician has an opportunity to practice health education as well as preventive medicine because the average diabetic sees his doctor far more frequently than the average nondiabetic Attention to eyeground examinations and electrocardiograms will provide an accurate appraisal of

(4) J A M A 169 910 914 F b 28 19 9

the onset and progress of accompanying complications Whether retinopathy and other degenerative diseases accompanying diabetes may be prevented or delayed by properly ordered treatment is not yet established Probably the answer will not be provided until the pathologic physiology of the degenerative lesions is completely understood and the causative factors clearly related to their effects

► [This study represents the best justification I know of for keeping close watch over patients who have glucose tolerance tests interpreted as being slightly abnormal or prediabetic It is interesting that this study has not shown any clear correlation between the tightness of control of diabetes and development of complications —Ed]

Diabetes Mellitus in Association with Primary Carcinoma of Pancreas Robert C Green Jr Archie H Baggenstoss and Randall G Sprague[5] (Mayo Found) reviewed 209 cases of primary carcinoma of the pancreas after autopsy to determine incidence of diabetes and relation between diabetes and the pancreatic tumor In 9 patients (4 3%) diabetes was noted before onset of symptoms of pancreatic carcinoma No conclusions could be reached as to whether prior presence of diabetes predisposes to development of carcinoma of the pancreas Presence of diabetes was not or could not be established in 168 (80 4%) patients

Another 32 patients (15 3%) were found to have diabetes after onset of symptoms of pancreatic carcinoma Among these patients no significant relation to type location and size of the neoplasm was noted In at least two thirds destruction of islet tissue by fibrosis tumor invasion or inflammation did not appear to be sufficient to account for presence of diabetes

It seems probable that the two factors of hereditary predisposition to diabetes and actual destruction of islet tissue owing to the presence of neoplasm although not shown to be individually significant in the entire series might in combination account for the observed instances of diabetes However other unrecognized factors cannot be excluded

Despite the fact that only 1 patient in 6 was proved to have diabetes after pancreatic carcinoma it is suggested that the possibility of such a lesion can be considered in any patient with persistent vague abdominal pain and newly discovered diabetes

► [The last sentence seem a b t strong I suppose it is fair to worry about th s type of tumor but it doesn t seem l kely to me that many more carci

(5) D b t 7 308 310 J ly A g 1958

nomas of the pancreas will be found in diabetics as a result of careful search than in nondiabetics who have comparable abdominal symptoms — Ed)

Quantitative Relationship between Insulin Dosage and Amount of Carbohydrates Utilized in Diabetic Persons Estimation of the insulin requirement of diabetic patients has to this day remained a purely empiric procedure with the goal to eliminate glycosuria and restore normal blood sugar levels Various authors have come up with greatly divergent G I ratios (G equals grams of glucose utilized I units of insulin injected) and claims have been made that 1 unit of insulin will metabolize as little as 1 2 Gm or as much as 22 Gm carbohydrate

Michael Somogyi and H V Goldwasser[6] (Jewish Hosp of St Louis) suggest that such divergencies are due to the fact that Allen and other authors have used the quantity of sugar lost in the urine as an index of insulin action instead of the amount utilized per unit of injected insulin The capricious variations in the extent of glycosuria in Allen s (1923) experiments actually showed no consistent relationship to changes in the composition of the diet but when the present authors computed from the protocols of Allen and of Porges and Adlersberg (1929) the amounts of carbohydrates that were utilized per unit of insulin which is the appropriate vardstick for the appraisal of insulin action an entirely different picture made its appearance

The results of these calculations revealed that the phenomenon which Allan (1924 25) observed in the depancreatized dog can be clearly recognized also in diabetic patients This pattern presents the fact that the magnitude of the G I ratio is largely dependent on the quantitative relationship between the amount of carbohydrates ingested and the amount of insulin injected a relationship which can be expressed in the form of a ratio

$$R = \frac{\text{grams glucose available in diet}}{\text{units of insulin injected}}$$

The G I ratio increases when R increases and shrinks when R decreases The range of variability under the influence of a changing R ratio is considerable Insulin action evidently yields progressively diminishing returns as the R ratio decreases

These facts help to explain the great divergencies in the

(6) Am J Med 26 165 168 F b y 1959

glucose equivalent of insulin (G I ratio) found by numerous authors each presenting his figure as a standard stoichiometric equivalent but they do not throw light on the mode of action of the R ratio

Exacerbation of Diabetes by Excess Insulin Action Michael Somogyi[7] (Jewish Hosp of St Louis) observed that exce s insulin action can produce hyperglycemia The impairment of carbohydrate tolerance as a sequel of hypoglycemia is explained by the fact that hypoglycemia stimulates the adrenal pituitary system to accelerate release of blood sugar raising hormones Increase in depth and duration of the hypoglycemic state intensifies this stimulus As a consequence the action of the blood sugar raising hormones can cancel out the action of injected insulin and tip the balance in favor of the former The result is a sharp rise in the glycemic level despite the presence of active insulin and exorbitant hyperglycemia and glycosuria after alimentation in this condition

When hyperglycemia due to excess insulin action is countered by increasing insulin doses the result is exacerbation of the diabetic syndrome This is manifested in extreme fluctuations of glycosuria with mounting peaks and ketonuria at the same time recurrent hypoglycemic reactions increase in severity

Man 26 was treated elsewhere 5 years previously for diabetic coma He was discharged on a diet of 60 Gm protein 125 Gm fat and 100 Gm carbohydrate with 50 unit of insulin daily Later the diet was changed to 70 Gm protein 140 Gm fat and 80 Gm carbohydrate and the insulin do age was lowered to 40 units because of frequent hypoglycemic attacks As the hypoglycemia was not mitigated by this step the carbohydrate ration was raised to 120 Gm The patient remained very unstable with frequent hypoglycemic reactions and variable degree often severe of glycosuria and ketonuria An increase in the insulin dosage to 75 units daily without a change in diet resulted in further deterioration

To avoid the distressing hypoglycemic reactions the daily insulin dose was lowered to 30 units (15 0 15) and the diet was changed to 70 Gm protein 50 Gm fat and 250 Gm carbohydrate However hypoglycemic reactions still occurred and ketonuria persisted Fractional urine samples revealed that the greater part of the sugar was excreted during the night The bulk of the nightly spill occurred after 4 a m The fraction between supper and midnight contained relatively little sugar and that between midnight and 4 a m showed only negligible amounts or none at all It appeared logical to try to stem the glycosuric tide at it inception with an injection of 15 units of insulin

(7) Am. J Med 26 169 191 F 6 ry 1959

nomas of the pancreas will be found in diabetics as a result of careful search than in nondiabetics who have comparable abdominal symptoms —Ed]

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(6) Am J Med 7 165 168 Feb y 1959

insulin are not reproduced by tolbutamide in responsive animals and human beings Moreover Seltzer and Smith (Proc Soc Exper Biol & Med. 100 171 1959) were unable to show a rise of plasma insulin after intravenous administration of tolbutamide to normal persons It seems safest at present to keep an open mind —Ed]

Oral Treatment of Diabetes Trial of Phenethyldiguanide (DBI) Insulin is irreplaceable in the treatment of diabetes and no satisfactory substitute has yet been discovered Search for substances that will lower the blood sugar when given orally revealed that certain sulfonylureas (notably carbutamide and tolbutamide) fulfilled this criterion However they were effective only in mild diabetes which agrees with the experimental finding that some functioning pancreatic islet tissue is necessary for them to exert full action One substance of the diguanide group (DBI) was found to produce hypoglycemia even in eviscerated or alloxan diabetic animals G H Hall Mary F Crowley and Arnold Bloom[9] (Whittington Hosp London) assessed its effectiveness in 40 patients with diabetes of all grades of severity

Dietary restriction alone for a week (where feasible) caused no significant fall in blood sugars whereas 50 mg DBI 3 times daily for several days led to a progressive fall in the mean blood sugars the lowest level being reached by the 6th day

In 5 patients whose lives depended on insulin ketosis developed rapidly when it was discontinued After DBI was given 11 of the other 35 patients showed intermittent acetonuria of greater frequency and concentration than before receiving DBI although the blood sugar was normal and no sugar was excreted This was not due to starvation since the patients had eaten consistently well Acetonuria also developed in most patients who became nauseated or who vomited while receiving DBI In 1 patient the paradoxical coexistence of ketonuria and aglycosuria was particularly marked

Man 51 underweight with newly diagnosed diabetes had thirst polyuria heavy glycosuria and acetonuria The initial noon blood sugar was 391 mg /100 ml After a week of DBI therapy the level fell to 80 mg /100 ml and urine sugar disappeared Daily excretion of acetone exceeded 1 Gm and the blood acetone was 10 mg /100 ml The DBI was discontinued with immediate reappearance of glycosuria Two days later acetone disappeared from the urine and the blood sugar rose to 300 mg /100 ml When DBI was started again glycosuria disappeared blood sugar fell to normal and acetone reappeared in the urine Continuation of DBI was considered unwise

(9) B M J 2 71 74 July 1 1958

at 4 a m This dose still proved to be too much Finally with two 10 unit doses a day the patient became consistently aglycosuric

► [The 2 preceding papers are very important and deserve study in their original form They teach at least two practical lessons that the adjustment of insulin dosage based only on the amount of glucose in the urine may not be physiologic and that overdoses of insulin may have deleterious effects which may not disappear for months after the dose is reduced It seems particularly important to emphasize that the number of plusses in the urine glucose test cannot give more than gross qualitative information about the amount of insulin needed The practice of adjusting insulin dosage by routinely adding a given amount of insulin for each plus is dangerous and unphysiologic and should be abandoned—Ed]

Studies on Action of Sulfonylureas in Liverless Dogs were made by G W Sobel J Rodriguez Inigo J V Morton and R Levine[8] (Michael Reese Hosp) Hepatectomized dogs maintained on infusions of glucose when given sodium tolbutamide in moderate doses showed a hypoglycemic response similar in magnitude to that in normal dogs Since the blood sugar is lowered in the face of unvarying input of glucose provided by constant infusion its hypoglycemic effect must depend on increased peripheral disappearance or utilization of glucose Such findings are at odds with the observations of Berson and Yalow who using C^{14} labeled glucose observed no increased disappearance of glucose during tolbutamide induced hypoglycemia Other investigators have also failed to demonstrate increased peripheral utilization of glucose following acute or chronic administration of the sulfonylureas

It has been previously shown in dogs and rabbits that total abdominal evisceration or complete pancreatectomy abolishes the hypoglycemic response to the sulfonylureas administered acutely Demonstration of a hypoglycemic response when only the liver is removed and the pancreas left intact lends further support to a pancreatotropic mechanism of action for the sulfonylureas The data reported however do not bear on possible effects these drugs may have on the liver when it is present in the body Similarity of response in intact and hepatectomized dogs seems to indicate that the liver does not participate to any great extent in production of hypoglycemia when moderate doses of tolbutamide are given acutely

► [The mechanism of action of the sulfonylureas is still debated However most observers now seem to feel that a major part of their action is release of insulin from the pancreas (or possibly from other sites of binding) If this is the case however one wonders why certain effects of

(8) Metabolism 7 2 2 6 May 1958

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(9) —B M J 2 71 74 J ly 1 1958

and insulin was given Although the patient had not complained during DBI administration he immediately commented on a sense of improved health with insulin

In the 5 patients with brittle diabetes DBI was substituted for insulin in doses varying from 150 to 250 mg /24 hours but it failed to prevent severe ketosis hyperglycemia thirst and polyuria Insulin had to be reintroduced Gastrointestinal disturbances developed in 26 of the 40 patients taking DBI Nausea anorexia abdominal discomfort vomiting and diarrhea were variable reactions but they were usually persistent enough for the drug to be withdrawn Symptoms usually appeared 3-4 days after the drug was started and were not related to hypoglycemia When DBI was discontinued the symptoms usually abated in 2 3 days

Dangers of Oral Therapy for Diabetes during Pregnancy One of the commonest causes of intrauterine death seems to be hypoglycemia The blood sugar level is always lower in the fetal circulation than in the maternal Therefore even a mild maternal hypoglycemia may prove lethal to the fetus

Annaliese Lass[1] (Hamburg Germany) observed a woman 40 in whom precoma with blood sugar level of 390 mg /100 ml developed during the 7th to 8th month of pregnancy while she was under oral therapy with BZ 55 (carbutamide) receiving 1 5 Gm daily Diabetes had been diagnosed early in the pregnancy A few hours after hospitalization she was delivered of a stillborn infant No cause for the fetal death was found The fetus was well developed the liver slightly enlarged Chemical investigations revealed a concentration of 1 8 mg /100 ml BZ 55 in the fetal liver clear evidence that the drug had passed through the placenta into the fetal circulation

It has been estimated that the placental permeability for sulfonamides is about 10% The same permeability is suggested for BZ 55 Whether a fetal BZ 55 blood level of 1 2 mg /100 ml affects the fetal carbohydrate metabolism or fetal development cannot be stated It must also be considered that the placental permeability increases toward the end of pregnancy Insulin because of its great molecular weight of 35 100 (the molecular weight of BZ 55 is only 271) does not pass the placental barrier and thus does not get into the fetal circulation

(1) Ge rt b u F u h 18 1167 1171 S pt be 195

The potentially harmful effects of BZ 55 on the fetus con traindicate its use during pregnancy

Hypoglycemic Effects of 1 (p Chlorobenzenesulfonyl) 3 N Propylurea Observations in Man Abraham M Tornow Myra K Zinke Philip Greenberg and Carroll M Leevy[2] found 1 (p chlorobenzenesulfonyl) 3 N propylurea (chlor

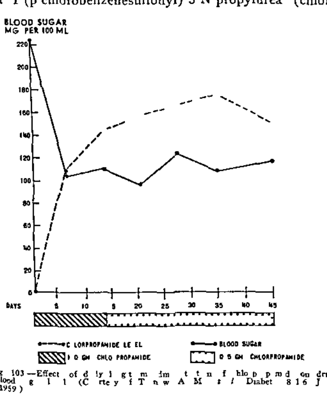


Fig 103 —Effect of d ly l g t m lm t t n f hlo p p m d on drug d blood g l l (C rte y f T n w A M t l Diabet 8 1 6 J F b 1959)

propamide) to be an effective hypoglycemic agent in diabetic patients It had only a slightly greater hypoglycemic effect than tolbutamide after a single 1 Gm dose However the drug appeared to be significantly more potent when given on a daily maintenance basis (Fig 103) It permitted stabiliza tion of diabetes in 2 patients who became refractory to tol butamide and in 4 with incomplete control on tolbutamide

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(2) D bet 8 1-6 J F b 1959

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15 after observation of 2 18 months Secondary resistance means that patients who have responded well to oral antidiabetic medication for 2 months or more become resistant to the drug This resistance appeared mainly in the first 6 months particularly among patients previously treated with insulin Nine had insulin treatment earlier Most patients with secondary resistance did not require a larger quantity of insulin after discontinuing oral treatment than before starting it Mean duration of the diabetes was 6 7 years among patients with secondary resistance and 2 5 years among the others

Secondary resistance may be due to a reversible collapse of the beta cells in the pancreas

► [The place of oral preparations in treatment of diabetes is not yet clear Many papers continue to report on this subject Among others of interest are a review in which 37 papers appear (Minerva med 49 1447 1958) the results of a questionnaire sent to 8 German diabetes centers (Deutsche med Wchnschr 83 1253 1958) a good historical review by Kleiner (Clin Chem 5 79 1959) and a discussion of the chemical modifications possible in DBI by Odell *et al* (A M A Arch Int Med. 102 520 1958) At present it appears that tolbutamide (Orinase®) is the safest material to use Chlorpropamide (Diabinese®) is probably a good deal more toxic and offers no advantage except its slower rate of catabolism If tolbutamide is given in divided doses it will apparently do anything chlorpropamide will do with greater safety Phenethyldiguanide (DPI) often causes gastrointestinal disturbances in doses too low to control the blood glucose Most studies evaluating this material consider it successful if a smaller amount of insulin is needed to control the patient than was needed without DBI This is clearly misleading however for merely reducing the insulin dose is no excuse for adding a new drug of uncertain long term toxicity to the treatment program It has been claimed that DBI may stabilize brittle diabetics in which case it might justifiably be administered Whichever of the oral preparations one uses the need for insulin during intercurrent illness operations or trauma must be kept constantly in mind Our chief problem in the control of hospitalized diabetic patients in recent months has been a result of attempts by uninformed physicians to perform surgery with no more protection than was offered by one of the oral antidiabetic preparations —Ed]

Diabetes and Pregnancy Results of 157 Pregnancies in Diabetic Women There is no substantial difference between diabetic and nondiabetic women in fertility and mortality due to pregnancy and labor but incidence of obstetric surgery and perinatal death is higher among diabetics M Worm[4] studied 147 diabetic women during 157 pregnancies that terminated in delivery of a viable infant at least 35 cm long and weighing at least 1 000 Gm

In the beginning of the study the aim was to keep blood

(4) D tsch m d W h sch 83 802 807 M y 2 1958

level of chlorpropamide and its effects on peripheral and hepatic venous sugar The drug tends to accumulate so that dosage adjustment is necessary to prevent a profound drop in blood sugar In 3 patients given a daily maintenance dose of 1 Gm for 2-4 weeks severe hypoglycemia associated with mental confusion tachycardia and sweating developed Reduction in the amount of the drug and frequency of administration prevented recurrent hypoglycemia

Clinical studies were done in 33 patients 18 with mild 7 with moderate 5 with severe and 3 with brittle diabetes Results of treatment with chlorpropamide for 6 weeks to 6 months showed the drug to be of value in the management of most of the patients with mild and moderate disease and in 2 with severe and 1 with brittle diabetes No evidence of dermal renal hepatic or hemopoietic toxicity was manifested during the period of study

A regimen consisting of an initial daily dose of 0 5 Gm chlorpropamide with a reduction or increase depending on the clinical response provided quickest control and fewest side actions Slight gastrointestinal reactions occurred in 6 patients receiving a daily dose of 1 2 Gm Best control was established by doing periodic determinations of blood sugar and sulfonamide levels

The mechanism of the hypoglycemia observed with sulfonylurea derivatives has been the subject of considerable controversy It has been suggested that these materials may act primarily on the pancreas to stimulate release of insulin or decrease elaboration of glucagon or that they exert their effect in the liver by facilitating normal hepatic processes or by inhibiting insulin antagonists Chlorpropamide appears to act similarly to carbutamide and tolbutamide Unlike phenethyldiguanide all these drugs cause an increase in liver glycogen and this effect has proved useful in the management of hepatic disease associated with diabetes

Secondary Resistance in Oral Treatment of Diabetes Oral antidiabetic drugs have been used in active therapy for over 2 years The types in use are carbutamide and tolbutamide The latter drug is more widely used because of lower toxicity and because it is not a sulfonamide

Gerhard Dotevall[3] (Varberg Sweden) treated 65 diabetics with these medications Secondary resistance occurred in

(3) Acta m d sc di 161 251 256 1958

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at age 18 At 22 when treated for coma pulmonary tuberculosis had been noted The first pregnancy had ended in mi carriage at 3 months After the miscarriage diabetes had been satisfactorily controlled

Blood pressure was 130/90 mm Hg but no cardiac enlargement was noted A trace of albumin was found in the urine and a few red blood cells were seen Early retinitis first appeared as a few small microaneurysms On a 2 300 calorie diet 32 units of soluble insulin before breakfast and 24 units of NPH insulin before the evening meal diabetes was satisfactorily controlled

At 25 weeks she was seen in the antenatal clinic and blood pres sure was 160/90 The urine contained 0 27 Gm albumin/100 ml Blood urea nitrogen level was 34 mg /100 ml Diabetes was difficult to control She had hypoglycemic attacks and other episodes of hyperglycemia

Although diabetes was kept under fairly satisfactory control mi nute retinal hemorrhages became visible at 34 weeks and blood urea nitrogen level rose to 38 mg As it was feared that continuation of the pregnancy would probably lead to intra uterine death and aggravate the mother s condition it was decided to terminate pregnancy at 35 weeks even though the fetus was obviously very small

The operation was performed under general anesthesia The infant weighed 2 lb 13 oz but was vigorous and appeared far more mature than usual for such a small baby The usual technic for lower segment cesarean section was followed The placenta contained many infarcts

The mother made a good recovery and insulin requirements di minished When she was discharged the blood pressure was normal but the urine still contained a trace of albumin and retinitis had progressed slightly

► [Dr Kelsey is braver than we are! The prognosis for both mother and baby is so grave in this situation that we usually recommend termination of pregnancy One wonders whether the development and progression of retinitis and the progression of nephropathy may not have been acceler ated by pregnancy It is hard that the mother in this situation buys the baby while shortening her own life —Ed]

Subclinical Diabetes Mellitus in Patients Presenting with Clinical Glomerulonephritis There are no clinical features pathognomonic of chronic glomerulonephritis although pro teinuria a typical urine sediment elements of the nephrotic syndrome and as the disease progresses renal failure are usually found Other diseases especially diabetes produce similar clinical findings In patients with renal disease the exclusion of diabetes mellitus may be difficult especially when there is no glycosuria and no elevation of the fasting blood glucose level The only possible reason for suspecting diabetes in such patients is the presence of nephritis

John D Arnold Alvin R Tarlov Benjamin Spargo and George J Brewer[6] (Univ of Chicago) studied 47 patients who had proteinuria and the urinary sediment of nephritis

(6) T A Am Phy 71 186 195 1958

sugar values between 100 and 200 mg/100 ml and patients free from acetone Delivery was carried out before term to prevent intrauterine death Diabetes itself was generally considered an indication for cesarean section In 7 women hormone treatment without progesterone was given according to White s scheme with no definite effect on the course of pregnancy or fate of the fetus

Because of a lowered kidney threshold for glucose during pregnancy the blood sugar levels aimed at during the beginning of the study led to considerable glucose losses through the urine and frequently to acidosis Hence during the 3d trimester insulin was increased up to 120 units on regular insulin divided into 3-4 daily doses This kept the blood sugar levels at 130 140 mg/100 ml rather constantly Occasional drops to 50 mg were tolerated without hypoglycemic reactions This regimen decreased the incidence of acidosis *considerably and hydramnios became rarer* Occasionally pre existing hydramnios regressed Large doses of insulin *apparently did not cause* edema

Increased insulin dosage made it possible to postpone rupturing the membranes to induce delivery until the 38th week and to limit abdominal cesarean sections to obstetric indications Wound healing after section was always normal Lethal eclampsia occurred in 1 patient Pre eclampsia mostly due to pre existing diabetic vascular changes occurred in 9 Carbohydrate tolerance almost always decreased usually *during the 3d trimester The carbohydrate metabolism* after delivery was about the same as before pregnancy Uncontrolled diabetes was not an indication of induction of labor

After absence of hypoglycemia in newborns of diabetic mothers was noted routine administration of glucose to these infants was discontinued Milk production was low and only occasionally could infants be breast fed

Obstetric operation was required in 75% The perinatal infant mortality of 19% was lowered to 13% with a stricter regimen of higher insulin dosage Incidence of malformations was 6 5%

Pregnancy Associated with Diabetic Nephropathy is reported by H A Kelsey[5]

Woman 26 with diabetes since age 14 was hospitalized early during her second pregnancy *Onset of renal damage had been suspected*

(5) J Obst & Gynaec Brit Emp 64 735 737 Oct be

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normal fasting blood glucose levels and no signs of other specific diseases Repeated *urinalyses showed no glycosuria* The urine of 40 patients showed birefringent fat in the sediment considered by some investigators as a part of diabetic kidney disease A standard test meal resulted in abnormal blood glucose levels (above 140 mg /100 ml) 2 hours later in 46% of these patients

Renal biopsies in the 40 patients showed the typical nodular lesion of Kimmelstiel and Wilson in 2 This is the most easily identified lesion but not the only renal lesion associated with diabetes mellitus A diffuse membranous lesion similar to membranous glomerulonephritis but with more *prominent endothelial cytoplasmic accumulations* can be clearly identified especially with the help of electron microscopy Such lesions were *found in 4 patients*

Of the 47 patients studied 18 had a 2 hour blood glucose level above 140 mg /100 ml 11 had a diabetic family history 8 had microaneurysms 2 have developed overt diabetes mellitus 2 had Kimmelstiel Wilson nodules 1 had a specific membranous lesion of diabetes 4 had nonspecific membranous lesions and 14 had vascular sclerosis

Apparently a *significant number of patients* with the classic clinical findings of chronic glomerulonephritis have in reality subclinical diabetes Diabetes should be considered a syndrome in which the demonstrable abnormality of *glucose* metabolism is only a part The underlying metabolic defect may cause *significant* and *identifiable renal pathology* before the defect in glucose metabolism is recognized The clinical discovery of this metabolic defect is in part dependent on stress and time

Diabetic Neuropathy Presenting as Initial Clinical Manifestation of Diabetes was observed by Max Ellenberg[7] (Mount Sinai Hosp New York) in 5 men and 2 women aged 21 74 Neuropathy *may be the presenting symptom* of diabetes mellitus and thus antedate appearance of other manifestations of the disease It is not dependent on the presence of prolonged *hyperglycemia* and *glycosuria and need not depend* on control of hyperglycemia for therapy

Any neurologic *picture compatible* with *or suggestive* of the syndromes associated with diabetic neuropathy and/or occurring *in* a patient with a family history of diabetes must

(7) A n Int M d 49 6 0-631 S pte b 19 S

be investigated for the possibility of diabetes mellitus Determination of the fasting blood sugar level is the least rewarding test in such situations It is much more productive to determine the 2 hour postprandial blood sugar level as a screening test and then to perform a glucose tolerance test as indicated Such an approach helped to solve unrecognized instances of diabetic neuropathy in 4 patients

Diabetes mellitus is not limited to a disorder of carbohydrate metabolism but has many separate features which are in some as yet undefined way related to each other much as are the spokes of a wheel These would include derangement of carbohydrate metabolism complications of pregnancy microangiopathy arteriosclerosis and neuropathy

► [Both of the preceding papers support the idea that some of the complication of diabetes can devel p before demonstrable or clinically perceptible abnormalities of carbohydrate metabolism appear If this is so can one be secure in claiming that poor control of the diabet s produces these abnormalities?—Ed]

Proliferative Retinopathy in Diabetes Mellitus Review of 847 Cases Howard F Root Stanley Mirsky and Jorn Ditzel[8] (Boston) studied 847 consecutive cases of proliferative retinopathy among diabetic patients It was found that retinopathy most commonly developed in persons with onset of diabetes early in life but it was not a necessary consequence of diabetes in young patient In patients whose diabetes began before the 20th year the average duration of diabetes before the discovery of proliferative retinopathy was 17 4 years and none developed the condition in less than 8 years It was usually the persons with onset of diabetes before age 40 years in whom insulin treatment and dietary management had been inadequate who presented the characteristic neovascularization of the retina

Early diagnosis and continuous control of diabetes may be of maximum importance in postponing and preventing proliferative retinitis since many patients are now known to have survived diabetes with onset in childhood for 20 30 years without evidence of retinal hemorrhages when diabetic treatment has been adequate The influence of sex and heredity appeared no different in diabetic patients with proliferative retinopathy than in those without

The association of proliferative retinopathy and malignant diabetic nephropathy or glomerulosclerosis of diabetes

(8) J A M A 169 903 909 F b 28 1959

is more intimate Hypertension and albuminuria although frequently absent at the onset almost invariably appeared within months or years after the retinopathy Death was predominantly due to the diabetic nephropathy Uremia was present in more than 50% of the patients In the older group although chronic glomerulosclerosis had been present the terminal event was in many instances coronary occlusion

The association of *retinitis proliferans* (proliferative retinopathy) with diabetic nephropathy and premature atherosclerosis in the young patient with severe diabetes further identifies this condition as one of the specific products of insulin deficiency and of the other metabolic defects which constitute the disease diabetes mellitus The postponement or prevention of proliferative retinopathy is possible by intensified efforts to find diabetes early and to provide for its continuous adequate treatment by skillful use of insulin and of dietary measures

Morphologic Changes in Blood Vessels of Diabetic Hamsters appear to represent acceleration of an aging phenomenon and are comparable to similar changes in blood vessels of the bulbar conjunctiva which have been described in patients with diabetes mellitus

Frederick N Sudak Samuel B Beaser Maurice H Shulman and George P Fulton[9] (Boston Univ) found that these changes in hamster cheek pouches increased with duration of the disease and were irreversible Alloxan was given in diabetogenic dose (60 70 mg/kg for males 70 80 mg/kg for females) to 26 male and 26 female hamsters Alloxan treated nondiabetic animals (that had received only 40 mg/kg alloxan on two occasions a week apart) and untreated animals served as controls No attempt was made to regulate blood sugar levels but insulin was given to sustain the animals and prevent fatal acidosis Cheek pouches were examined about once a month for a year After 90 120 days in diabetic hamsters fusiform distentions of the walls of the veins resulting in sacculations appeared at junctions of veins with larger vessels draining the cheek pouch (Fig 104) but did not appear on other vessels At least 2 sacculations were present in each cheek pouch None was found in the controls After 180 days of diabetes distentions appeared

[9] [illegible] 62 679 682 My 1958



Fg 104—S culation t venou j ction ed ed from ×77 (Courtesy f S dak F \ et l Endocri logy 6 679-68 M y 1958)

in the arterial walls of cheek pouches in 5 of 23 surviving animals and the number of venous sacculations had increased Of 6 untreated controls 2 showed a ingle venous sacculation none was present in alloxan treated controls One hamster remained diabetic for 370 days and showed 21 venous sacculations and 1 arterial sacculation At this time of 10 controls 7 (including 3 untreated) had 1 5 sacculations The ratio of arteriolar to venular diameters remained constant in all the animals during the experiment In 8 animals that reverted to normoglycemia no lesions appeared to be reversible

► [If retinopathy and other vascular changes are a result of hyperglycemia or insulin deficiency one might hope to be able to reproduce these changes in experimental animals This has not been easy to do Sudak s experiments did not produce typ cal diabetic changes but perhaps the blood vessels of the hamster cheek pouch do not react in the same way as the vessels of the human eye or kidney —Ed.]

Visual and Vital Prognosis in Retinopathy of Pancreatic Diabetes In examination of 1 403 diabetics Appelmans E Van Hoonacker and H Daels[1] (Louvain) found 460

(1) Ar h opht 18 7 1 733 Oct Nov 1958

is more intimate Hypertension and albuminuria although frequently absent at the onset almost invariably appeared within months or years after the retinopathy Death was predominantly due to the diabetic nephropathy Uremia was present in more than 50% of the patients In the older group although chronic glomerulosclerosis had been present the terminal event was in many instances coronary occlusion

The association of retinitis proliferans (proliferative retinopathy) with diabetic nephropathy and premature atherosclerosis in the young patient with severe diabetes further identifies this condition as one of the specific products of insulin deficiency and of the other metabolic defects which constitute the disease diabetes mellitus The postponement or prevention of proliferative retinopathy is possible by intensified efforts to find diabetes early and to provide for its continuous adequate treatment by skillful use of insulin and of dietary measures

Morphologic Changes in Blood Vessels of Diabetic Hamsters *appear to represent acceleration of an aging phenomenon and are comparable to similar changes in blood vessels of the bulbar conjunctiva which have been described in patients with diabetes mellitus*

Frederick N Sudak Samuel B Beaser Maurice H Shulman and George P Fulton[9] (Boston Univ) found that these changes in hamster cheek pouches increased with duration of the disease and were irreversible Alloxan was given in diabetogenic dose (60 70 mg /kg for males 70-80 mg /kg for females) to 26 male and 26 female hamsters Alloxan treated nondiabetic animals (that had received only 40 mg /kg alloxan on two occasions a week apart) and untreated animals served as controls No attempt was made to regulate blood sugar levels but insulin was given to sustain the animals and prevent fatal acidosis Cheek pouches were examined about once a month for a year After 90 120 days in diabetic hamsters fusiform distentions of the walls of the veins resulting in sacculations appeared at junctions of veins with larger vessels draining the cheek pouch (Fig 104) but did not appear on other vessels At least 2 sacculations were present in each cheek pouch None was found in the controls After 180 days of diabetes distentions appeared

(9) Endocrinology 62 679 68 May 1958

1/10 in both eyes) occurred in 4 56% of the 460 patients with retinopathy

Among 209 patients followed 1 15 years 15% died within a year after diagnosis of retinopathy 42% within 5 years 50% within 10 years and 72% after 15 years Mortality was not significantly different in the two sexes Average duration and minimal survival was higher (59 months) in patients aged 40-60 than in those older and younger (46 months) The presence of retinopathy increases the likelihood of death from cerebral vascular accident in diabetic patients

Hypoglycemic Sulfonamides and Diabetic Retinopathy *J F Cuendet J R Hofstetter C Ramel and S Nahman*[2] (Univ of Lausanne) report a clinical study on 46 diabetic patients treated on an average of a year with hypoglycemic sulfonamides—Invenol carbutamide or tolbutamide None received insulin during treatment with the antidiabetic preparation and all were examined ophthalmoscopically before and after treatment Most patients were over age 50 and had severe diabetes Of the 46 22 had previously been treated with insulin

Contrary to expectations the evolution of retinopathy was influenced no more favorably by antidiabetic sulfonamides than it was by insulin Retinopathy progressed in 11 patients (1 of whom had been treated by cortisone outside the clinic) and appeared in 4 during treatment It appears that previous insulin treatment may play a role in the evolution of retinopathy during treatment with antidiabetic drugs Among the patients previously given insulin retinopathy progressed in 7 (seriously in 2) whereas progression was noted in only 4 of the group not given insulin The only 2 patients in whom retinopathy improved had not previously received insulin

It should be noted however that the duration of diabetes among the patients previously treated with insulin averaged 8 years in the group without insulin it averaged 4¼ years On the other hand it was also observed that retinopathy worsened in well controlled diabetics as well as in those patients in whom glycemia and glycosuria were not always satisfactory

► [Although it is too early to be sure t appears that the oral antidiabetic agent are not of special value in pat ents with retinopathy —Ed]

(2) Ophth Int 1 g 135 530 53 1958

(32 7%) with retinopathy 78 of whom were observed regu larly for several years Of these *64* (*35 men*) had visual acuity of over ⅓ in one eye In 9 vision remained good for over 6 years and in 5 for over 8 years (ages at onset of ret inopathy were 40 42 43 51 and 63) In these cases function al integrity was conserved for 7 years but deterioration was evident at the beginning of the 8th year Sex does not appear to influence the visual prognosis of pure retinopathy Con versely age of appearance of retinopathy is important In patients under age 20 good vision has persisted over 63 months in those aged 20 39 53 months aged 40-59 45 months and over 60 years 35 months Average decrease in vision is also more marked in older subjects In those under 40 average decrease in 5 years was 0 13 whereas in those over 60 it was 0 33 Sclerosis and capillary fragility increase with age and play a significant role in production of macular changes

Although progression of diabetic retinopathy is generally gradual complications may result in sudden visual loss that may end in blindness these are more frequent in periods of decompensation of the diabetes

In 93 eyes of 70 patients (21 of whom became blind in both eyes) visual acuity was reduced to less than 1/10 In 66 vision was changed as a result of capillary dilatations exu dates and hemorrhages in the macular region The location of the initial lesion may influence the relationship between retinopathy and visual acuity An exudate or small hemor rhage in the fovea at the beginning may result in rapid loss of vision during the first months In 1 patient vision was re duced to 1/100 in 13 months and in another to 1/50 in 24 months Total or partial thrombosis of the central retinal vein accounted for serious visual loss in *7* of the *93* eyes *All* thromboses were unilateral and were in the left eye in 6 in stances Hemorrhages into the vitreous caused visual loss in 10 eyes In 6 some visual function was regained after ab sorption of the hemorrhage One patient aged 62 whose vi sion was reduced to 1/20 had recovery to 1/3 in 8 months Proliferating retinitis in 10 cases resulted from vitreous *hemorrhages* with vascularization

Retinopathy caused blindness in 1 49% of the 1 403 dia betics or in 3 1% of the 2 806 eyes Blindness (vision under

eral mild hypoglycemic reactions occurred and the dose of insulin was decreased from 62 to 50 units daily After the *three periods of reduced doses of insulin it was found that* administration of 40 units daily was adequate to control glycosuria while shortly before the termination of the study he was having some mild reactions on as little as 32 units His weight appeared to be maintained by the diet Shortly after returning home his insulin requirement increased to the original 60 units daily

Despite the pronounced glycosuria when the dose of insulin was reduced significant acidosis did not develop The CO_2-combining power decreased to a low point of 24 mEq/L at the end of the third period of reduction of the insulin dose but it had been 29 mEq only 4 days previously Pronounced loss of weight and dehydration were noticeable Qualitative tests for acetone in the urine gave positive reactions for the greater part of this time but the reactions were occasionally negative Values for blood glucose were extremely erratic and the degree of control is best shown by the chart of urinary excretion of glucose (Fig 105)

Pronounced hypercalciuria was present throughout the study This increased by an insignificant increment during the three periods of the reduced dose of insulin The mean daily urinary excretion of calcium during control periods was 345 mg during periods 3 4 and 5 it was 440 mg The difference was not statistically significant However an increase in the fecal excretion of calcium during succeeding control periods resulted in an over all worsening of the negative calcium balance

The data regarding urinary excretion of glucose values for serum calcium phosphorus and alkaline phosphatase and the balance data for calcium nitrogen and phosphorus are given in Figure 105 These studies failed to show any clinically significant relationship between the state of diabetic control and calcium balance

Severe Hypoglycemia Secondary to Nonpancreatic Fibrosarcoma with Insulin Activity is reported by J Thomas August and Howard H Hiatt[4] (Harvard Med School) in a woman aged 82 with frequent and protracted episodes of hypoglycemia that ceased when a large intrathoracic fibrosarcoma was removed No evidence was noted of adrenal

(4) N w E gl d J Med 58 17 20 J 2 1958

Metabolic Studies of Patient with Osteoporosis and Diabetes Mellitus are reported by Clifford F Gastineau and Marschelle H Power[3] Studies in diabetic acidosis have suggested the possibility that poorly controlled diabetes could result in a chronic wastage of calcium and nitrogen and de

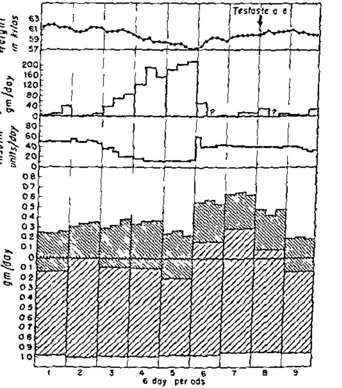


Fig 105 —Effect f d t n f ulnad f e f t st t r uri y gl e d c l m balan e n p t e t w th teopo o s d di bet s Calcium t ke i d ted by l w t l bel w e b e l o tp t by total amou t xtend g pwa d fr m take] Coa e hat h ng ep t fec l exc t on & b tch g nary xc et n (Court y of G st e C F a d P w r M H P oc Staff Me t Mayo Cl n 34 165 172 Ap 1 1959)

mineralization of the skeleton Metabolic studies were conducted on a man 34 who had had diabetes mellitus for 19 years and disabling back pain for 2 He also had an extensive demineralizing bone disease best described as osteoporosis

During the metabolic studies the decrease in insulin requirement was striking During the first 6 day period sev-

(3) Proc Staff Meet Mayo Cl 34 165 172 Ap 1 1959

CALCIUM PHOSPHORUS AND THE PARATHYROID GLANDS

Observations on Patients with Hypercalcemia Exemplifying Problems in Differential Diagnosis Especially in Hyperparathyroidism Hypercalcemia may occur in a variety of clinical situations and conditions including laboratory error neoplastic disease sarcoidosis hypervitaminosis D milk alkali syndrome hyperthyroidism idiopathic hypercalcemia of infants and acute skeletal atrophy of disuse as well as in hyperparathyroidism Each may be accompanied by hypophosphatemia The diagnostic problem is to differentiate hyperparathyroidism which requires surgery from other causes of hypercalcemia

In recent studies on hyperparathyroidism some investigators have deemed the response to intravenous calcium measurement of tubular reabsorption of phosphorus (TRP) and the effect of cortisone to be of diagnostic value This opinion is questioned by William C Thomas Jr Thomas B Connor and H Gemmell Morgan[5] (Johns Hopkins Univ) on the basis of studies on 28 patients 18 with hyperparathyroidism (subsequently proved by operation) and 10 with hypercalcemia due to other causes

All 28 responded to intravenous calcium similarly regardless of the cause of the hypercalcemia Phosphorus reabsorption calculated as per cent TRP or as milligrams per 100 ml glomerular filtrate was quite similar in the two groups The TRP in 7 patients who did not have azotemia or hypercalcemia ranged from 84% to 91% of the filtered phosphorus (within normal limits) In 8 patients with hyperparathyroidism only 2 of whom had slight azotemia the TRP varied from 55% to 86% whereas in 7 patients with hypercalcemia from other causes the values were also low ranging from 37% to 81% In this latter group azotemia was present in all but 1 and the creatinine clearance was generally much lower

Cortisone was administered to 15 patients In 3 with hyperparathyroidism and in 6 with hypercalcemia of other origin the serum calcium did not decrease The other 6

(5) J Lab & Cl Med 5 11 19 July 1958

pituitary or hepatic disease, any of which may give rise to hypoglycemia

Hypoglycemia may have resulted from diminished hepatic production of glucose or increased peripheral utilization. Demonstration of normal liver function studies, ample liver glycogen and normal hepatic glucose-6-phosphatase activity made the former possibility seem unlikely. The rapid fall in blood sugar level observed during the preoperative glucose tolerance test was consistent with increased peripheral utilization of glucose. This hypothesis was further strengthened by demonstration of insulin activity in the tumor in an amount calculated to be three times that reported in the pancreas of a normal woman.

The diabetic glucose tolerance curve noted on the 6th postoperative day and the normal result on the 19th day suggest an extrapancreatic source of insulin. It may be that the pancreatic islet tissue underwent some degree of functional atrophy during the time the tumor was secreting insulin and therefore was incapable of responding normally to a glucose load during the immediate postoperative period. Transient hyperglycemia has also been reported after removal of functioning pancreatic islet cell tumors. A similar mechanism may account for the fact that the tumor was present for at least many months before onset of hypoglycemic episodes. It is possible that during the asymptomatic period the lesion produced insulin in a quantity no greater than the requirements of the patient and that simultaneously pancreatic insulin secretion was diminished by an amount equal to that elaborated by the tumor. During the 3 months before surgery so much insulin was produced by the tumor that hypoglycemia occurred after as short a fast as 3 hours.

In the light of present concepts of carbohydrate metabolism, these clinical and laboratory observations are consistent with an insulin-secreting extrapancreatic tumor as the mechanism of hypoglycemia in this patient.

► [I selected this paper both because this syndrome is currently producing a good deal of interest and because this is the only case I know in which a hypoglycemia producing substance(s) was isolated from the tumor. Other recent reports in which such substances were not isolated include papers by Boss (Schweiz Ztschr allg Path 29 232 1959) and Sellman (New England J Med 260 847 1959). Klein reports a case (A M A Arch Int Med 103 273 1959) but no tissue was available for extraction. Further attempts to isolate a hypoglycemic agent should be made when such tumors appear in the future.—Ed.]

calcium metabolism Mepilin (0 01 mg ethinyl estradiol with 3 mg methyltestosterone/tablet) was given in an initial dose of 12 tablets daily This treatment produced rapid rise in weight and a drop in serum calcium level to 8 4 mg /100 ml Urinary output of calcium also fell to normal and alkaline phosphatase level rose to 6 King Armstrong units Since the weight continued to rise and general condition was satisfactory dose of Mepilin was decreased and intake of calcium increased Serum calcium level then returned to normal

► [One cannot help wondering (diffidently) whether perhaps this patient may have had hyperthyroidism Certainly the low phosphorus does not fit too well into the picture of osteoporosis It is easy to understand why the authors were puzzled —Ed]

Idiopathic Hypoparathyroidism and Pseudohypoparathyroidism Case Reports and Review of Literature are presented by David Bronsky Daniel S Kushner Alvin Dubin and I Snapper[7] (Chicago) Drake and co workers in 1939 set forth the following criteria for diagnosis of idiopathic hypoparathyroidism in the absence of a history of thyroid gland surgery low serum calcium level high serum inorganic phosphorus level absence of roentgenologic signs of rickets and osteomalacia chronic tetany and absence of renal insufficiency *steatorrhea chronic diarrhea and alkalosis* Albright and associates divided hypoparathyroidism of unknown cause into two forms both of which fulfill these criteria One form still called idiopathic hypoparathyroidism responds readily to parathyroid extract whereas the other designated pseudohypoparathyroidism does not Patients with the latter type of disease have also presented brachydactylia and subcutaneous bone formation

Idiopathic hypoparathyroidism has been found to affect the sexes equally Average age at onset is 17 but onset may occur at any age up to 60 years Familial hypoparathyroidism is uncommon Short stature is common but height may be above average The face and body build are usually normal Papilledema is frequently present Autopsy findings usually reveal the parathyroid glands either replaced or absent

In pseudohypoparathyroidism the ratio of women to men is 2 1 Average age at onset is 8½ years and the disease usually begins before age 20 Familial hypoparathyroidism and skeletal defects are common The stature is invariably short the face round and the body stocky Mental retardation dental abnormalities and skeletal deformities apart from brachydactylia are common Exploration of the neck reveals hyper

(7) M d 37 317 3 D embe 1958

none of whom had hyperparathyroidism became normocalcemic after 5 14 days of treatment

The results suggest that these procedures are of limited significance in the differential diagnosis of hypercalcemia

► [This paper and similar one by Schwartz (M Clin. North America 43 497 1959) go a long way toward debunking the current ideas about the clinical and laboratory evaluation of hypercalcemia. No single test makes the correct diagnosis and even careful evaluation of various tests together with close clinical observation may not yield the answer Although some problems are easy to evaluate some patients especially those with impaired renal function may defy the best efforts which can be brought to bear on the problem at present An example of this is illustrated in the next case—Ed]

Acute Osteoporosis with Hypercalcemia without previous bone disease was observed by A Stuart Mason[6] (London Hosp)

Woman 22 was hospitalized She had had a *motor accident* after which her general condition had steadily deteriorated Fourteen weeks after injury weight had dropped 50 lb tachycardia had persisted and anorexia vomiting lethargy and muscular weakness had predominated Radiography had revealed osteoporosis of the legs lumbar spine and pelvis Serum calcium level had been 16.2 and serum phosphorus 2 8 mg /100 ml and alkaline phosphatase 9 King Armstrong units The parathyroid glands had been explored but no adenoma had been found One parathyroid gland had been removed but had been found normal on histologic examination Postoperatively the serum calcium level had fallen rapidly and the condition had improved but improvement had been short lived and all previous symptoms had returned 2 weeks after operation The serum calcium level had again risen to 16 mg /100 ml

When the patient was first seen blood values were calcium 14.2 and 15 6 mg and phosphorus 1 9 and 2 3 mg / 100 ml The urinary excretion of calcium was 383 mg in 24 hours Radiography showed osteoporosis of the legs pelvis and lumbar spine The original fractures had not healed

As the serum phosphatase level was not increased the high serum calcium level could not be attributed to hyperparathyroidism but seemed more probably the result of bony fractures and immobilization An intensive program of active movements was started At the same time calcium intake was reduced to 500 mg daily and 2 weeks later to 250 mg daily

On this regimen she made steady progress vomiting and thirst disappeared appetite returned and weight increased The serum phosphorus level quickly rose to normal but the serum calcium level fell slowly until it remained steady at 12 mg /100 ml The calcium balance remained negative the urinary excretion of calcium being 372 mg in 24 hours after 2 weeks on an intake of 250 mg in 24 hours This failure to return to completely normal despite adequate mobilization was evident 25 weeks after injury In a further effort to improve the

(6) Lancet 1 911 912 May 4 1957

The operative technic for transplantation varied in each patient in accordance with the site used for vascular anastomoses The tissues were taken from full term or premature newborn infants or infants aged up to 21 months

THE OVARY

► The Metabolism section has not previously included a separate division on The Ovary and it is not likely that the presentation of ovarian problems will be continued in future years It happens however that this year a group of papers have appeared presenting cases in which ovarian tumors produced syndromes like those produced by endocrine tumors in other parts of the body They are grouped together to emphasize the fact tha the ovary can do many thing —Ed

Cushing s Syndrome Associated with Adenocarcinoma of Ovary is reported by Victor Parsons and Barbara Rigby[9] (King s College Hosp London) Association of Cushing s syndrome with neoplasia in sites such as the thymus bronchus pancreas or ovary has been observed The authors case also shows that the excessively high concentrations of circulating steroid responsible for the clinical syndrome result from oversecretion rather than from failure of inactivation in the liver

Woman 64 with abdominal fullness for 2 months showed gross ascites and a hard fixed mass high in the left fornix of the vagina external genitalia were normal Blood pressure varied between 190/105 and 170/90 mm Hg A right ovarian ma s was excised and deposit of growth were noted in the pouch of Douglas and around the bladder The omentum and liver seemed free from deposits The excised mass consisted of ovarian tissue this was the site of a semicystic growth that on section proved completely anaplastic except in some areas where a poorly differentiated adenocarcinoma was noted

Glycosuria was first noted 3 days after operation The blood sugar level 2 hours after a glucose meal was 334 mg /100 ml Later other facets of Cushing s syndrome appeared—ankle edema purplish petechiae over both legs plethoric facies and hair on the lip and chin The blood pressure slowly rose to 200/120 Subsequently she received deep x ray therapy to the pelvis Diabetes was controlled with difficulty A urinary infection developed and she died 4 months after the first signs of Cushing s syndrome appeared Plasma concentration and urinary output of adrenocortical hormones was high No evidence of failure of hepatic inactivation was noted until the terminal stage

At autopsy the adrenals showed increased thickness of the cortex Sections of the excised ovarian tumor showed an anaplastic carcinoma

(9) Lancet 992 994 Nov 8 1958

plastic parathyroid glands The patient with this type of disease barely doubles hourly phosphate output in response to the Ellsworth Howard test whereas the patient with idiopathic hypoparathyroidism shows a 4½ fold increase and controls a 2½ fold increase Measurement of the glomerular filtration rate and determination of the phosphate clearance and the per cent tubular reabsorption of phosphate is recommended to aid interpretation of the test

The hypoparathyroid state in pseudohypoparathyroidism can usually be shown to be associated with renal end organ resistance to the action of parathyroid extract and therefore probably to endogenous parathyroid hormone Some authors have attributed the syndrome of pseudohypoparathyroidism to several unrelated but often simultaneously occurring genetic disorders

Transplantation of Homologous Thyroid and Parathyroid Glands is reported by Julian A Sterling[8] (Albert Einstein Med Center Philadelphia) Though chronic tetany due to hypoparathyroidism usually responds to medical therapy after thyroidectomy certain patients become refractory or do not respond to massive amounts of calcium vitamins (including AT 10) and parathyroid hormone One patient required 40 cc of 10% calcium gluconate intravenously 5 or 6 times daily during ovulation or menstruation In addition many patients require 2 4 gr thyroid extract daily by mouth

Four patients with hypoparathyroid tetany and hypothyroidism for 11 15 years after thyroidectomy were treated by transplantation of homologous thyroid and parathyroid glands In 1 the procedure was attempted twice but failed both times The other 3 who received the homologous transplants with use of anastomoses between the host and the vascular pedicles of the donor no longer showed signs or symptoms of hypoparathyroid tetany and 1 was free from pre existing hypothyroidism The other 2 though they were not taking thyroid extract and were reasonably free from symptoms of hypothyroidism did not have evidence of thyroid cell activity in the transplant Presumptive clinical evidence indicated that parathyroid cell function was present in the 3 patients and was due to persistence of homologous gland tissue which was transplanted 1½ 2½ and 5 years previously

(8) T n pl B ll 5 50 52 Ap 1 1958

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(8) T pt B B 5 50-3 Ap 1 1958

literature In most cases thyroid tissue was histologically normal In 108 of the 233 cases reviewed inclusions were associated with a complex teratoma of the ovary In 56 simple thyroid inclusions were found within the wall of an ovarian cyst (simple teratoma) In 69 cases the tumor was a pure ovarian goiter containing thyroid tissue only

In 9 cases cure of hyperthyroidism followed removal of the ovarian goiter In 3 removal of the ovarian tumor did not relieve toxic symptoms and thyroidectomy was necessary In 1 case a positive radioactive iodine test showed fixation in the thyroid indicating that the tissue was excessively active Only 8 of 233 tumors were proved to be malignant some doubtful cases were eliminated Some of these tumors recurred after removal and others metastasized Death was reported in only 4 cases of malignant tumor

Ovarian goiter is seldom diagnosed before operation but is discovered on pathologic examination of removed tissue This is not surprising in the case of thyroid inclusions in simple or complex ovarian cysts or in nonfunctioning ovarian goiters but it has been true also in cases in which thyrotoxicosis is present In 1 case of malignant ovarian thyroid the BMR before operation was +71% In a case in which hyperfunctioning thyroid tissue in the ovary is suspected a test with radioactive iodine might be confirmatory The physiopathologic condition of the cervical thyroid gland could be determined at the same procedure In determining the presence of thyroid cancers of the ovary search for metastases is important particularly in the long bones Fixation of radioactive iodine is valuable in tracing the presence of regional or generalized metastases

Carcinoid Tumor within Ovarian Teratoma in Patient with Carcinoid Syndrome (Carcinoidosis) Clinical Picture and Metabolic Studies before and after Total Resection of Tumor are presented by A Thorson A Hanson B Pernow S Soderstrom J Waldenstrom S Winblad and H B Wulff[3] Before surgery the patient had a well developed carcinoid syndrome with flushing changing blotchy cyanosis telangiectasia pellagra hyperperistalsis edema ascites pleural exudate and right sided valvular heart lesions She had also diarrhea borborygmi and crampy pain as evidence of episodic hyperperistalsis Asthma was the only common

(3) A ta m d sc d 161 495 50 1958

with no structural features to suggest that it was an arrhenoblastoma or a masculinovoblastoma

The authors assume that the stress of severe long standing malignant disease might have provoked hyperactivity of the adrenal of sufficient intensity to provoke Cushing's syndrome

Case of Masculinizing Ovarian Tumor Use of Corticosteroid Inhibition Test in Diagnosis is reported by May Cohen Ernest J Maltby and John C Laidlaw[1] (Univ of Toronto)

Woman 38 had virilism and elevated urinary excretion of 17 ketosteroids (14 1 19 8 mg /24 hours) but no abdominal or pelvic mass that could be detected on clinical or radiologic examination Administration of prednisone resulted in a slight fall in the 17 ketosteroid excretion which averaged 3 7 mg /day This fall was definitely smaller than had been previously observed in patients with adrenal hyperplasia but proportionately greater than that noted in patients with adrenal carcinoma This is the kind of response that might be predicted in the presence of an ovarian tumor Hence a provisional diagnosis of masculinizing ovarian tumor was made On pelvic laparotomy an arrhenoblastoma of the left ovary was found Postoperatively, urinary 17 ketosteroid excretion fell to within normal limits menstrual periods returned hirsutism diminished and blood pressure fell from 160/110 to 135/90 mm Hg

Because of the results obtained from the corticosteroid inhibition test in this patient it may be possible to differentiate adrenal from ovarian tumors as a cause of virilism when as is often the case they cannot be localized on physical or radiologic examination Such a test would be of little value if the ovarian tumor secreted a large amount of 17 ketosteroids e g over 30 mg /24 hours and if this amount tended to vary greatly from day to day In the presence of a masculinizing ovarian tumor with normal total 17 ketosteroid output the corticosteroid inhibition test would be of little diagnostic value

► [I doubt that an intermediate response to adrenal suppression will prove to be very helpful in delineating this group of patients since the range of the normal response is so great that it may prove hard to separate off the intermediate group Moreover this patient is a little unusual since most women with arrhenoblastomas have a normal rather than elevated 17 ketosteroid excretion —Ed]

Types Prognosis and Diagnosis of Thyroid Tumors of Ovary are discussed by P Brocq C Rouvillois and J Gauchez (Paris) on the basis of 2 previously unpublished cases 4 cases from the French literature and 233 from other world

(1) J Clin Endocrin 1 18 794 797 J 1 1958
( ) Pres med 67 165 167 Jan 28 1959

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(3) Acta m d. sc nd 161 495 05 1958

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The authors assume that the stress of severe long standing malignant disease might have provoked hyperactivity of the adrenal of sufficient intensity to provoke Cushing's syndrome

Case of Masculinizing Ovarian Tumor Use of Corticosteroid Inhibition Test in Diagnosis is reported by May Cohen *Ernest J Maltby and John C Laidlaw*[1] *(Univ of* Toronto)

Woman 38 had virilism and elevated *urinary* excretion of 17 ketosteroids (14 1 19 8 mg /24 hours) *but no abdominal or pelvic* mass that could be detected on clinical or radiologic examination Administration of prednisone resulted in a slight fall in the 17 ketosteroid excretion which averaged 3 7 mg /day This fall was definitely smaller than had been *previously observed in* patients with *adrenal hyperplasia but proportionately greater than that noted in* patients with adrenal carcinoma This is the kind of response that might be predicted in the presence of an ovarian tumor Hence a *provisional* diagnosis of *masculinizing ovarian tumor* was made On pelvic laparotomy an arrhenoblastoma *of the left ovary was found* Postoperatively urinary 17 ketosteroid excretion fell to within normal limits menstrual periods returned hirsutism diminished and blood pressure fell from 160/110 to 135/90 mm Hg

Because of the results *obtained* from the corticosteroid inhibition test in this patient, *it may* be possible to differentiate adrenal from ovarian tumors as a cause of *virilism* when as is often the case they cannot be localized on physical or radiologic examination Such a test would be of little value if the ovarian tumor secreted a large amount of 17 ketosteroids e g over 30 *mg /24* hours and if this amount tended to vary *greatly from day to day* In the presence of a masculinizing ovarian tumor with normal total 17 ketosteroid output the *corticosteroid* inhibition test would be of little diagnostic value

► *[I doubt that an intermediate response to adrenal suppression will prove to be very helpful in delineating this group of patients since the range of the normal response is so great that it may prove hard to separate off the "intermediate group Moreover this patient is a little unusual since most women with arrhenoblastomas have a normal rather than elevated 17 ketosteroid excretion —Ed]*

Types *Prognosis* **and Diagnosis of Thyroid Tumors of Ovary** are discussed by P Brocq C Rouvillois and J Gauchez (Paris) on the basis of 2 *previously unpublished* cases 4 cases from the French literature and 233 from other world

(1) J Cl Endocr 1 18 794 797 Jul , 1958
( ) Pr se m d 67 165 167 Jan 28 1959

Montreal) in 6 subjects 3 with dwarfism 1 who had hypophysectomy because of metastatic carcinoma of the breast 1 with postmenopausal osteoporosis and a normal medical student The effects of growth hormone on nitrogen potassium phosphorus calcium and sodium balances on urinary excretion of aldosterone 17 ketosteroids and 17 hydroxycorticosteroids and on the oral glucose tolerance curve were determined The human growth hormone was prepared from pituitaries obtained at autopsy and the monkey growth hormone from pituitaries made available as a consequence of

CASE	N	Ca	P	Na	K	GTC	ALDOSTERONE
PANHYPOPITUITARISM (AM)	+	+	+	+	+	+	+
(GL)	+	O	O	O	±	+	+
(DM)	+	±	±	+	+	+	
NORMAL	O	O	O	O	O	O	O
Ca OF BREAST HY OPHYSECTOM ED	±	±	±	±	±	+	O
OSTEOPOROSIS	O	±	±	O	O	+	+

Fg 106—M t b l ff t f h m g wth h mo + g h q l pon ± m ll d l d fi t h g d 0 n po (O ld t d m t w t l bl) (C rt y f B k J C t l A I t M d 49 1093 1105 N mb 1958)

the poliomyelitis vaccine program The growth hormone in a slightly acid pH was administered intramuscularly every 6 or 12 hours The injection produced no local reactions but 1 patient became oliguric on the 5th day and anuric on the 6th day of administration of the monkey growth hormone in a dose (20 mg 4 times a day) now considered excessive

Growth hormone administration appeared to result in three distinct types of physiologic change perhaps due to three separate components in the growth hormone preparations studied These are summarized in Figure 106 and it is apparent that the changes are independent of each other There is the anabolic effect which can be subdivided into a retention of nitrogen and potassium the intracellular elements found in muscle and parenchymal tissues and a retention of calcium and phosphorus constituents necessary for increase in mass or repair of bone There is some evidence that this may occur in the absence of significant nitrogen re

sign that was absent The 5 hydroxytryptamine (5 HT) 5 hydroxyindolacetic acid (5 HIAA) and histamine were elevated in blood and urine The pellagra disappeared after niacin treatment After surgery the valvular affection probably progressed and the edema diminished to some extent The other manifestations disappeared immediately and had not recurred 17 months later

The mechanism leading to pellagra might be a disturbed tryptophan metabolism inducing depression of niacin synthesis or a disturbed intestinal function causing decreased resorption from the intestine The mechanism behind pellagra in the authors patient could not be definitely identified Probably both factors participated because she had long standing diarrhea and a protein disturbance with a low serum albumin level The protein disturbance might suggest disturbed niacin synthesis as well The disappearance of hyperperistalsis immediately after resection of the ovarian tumor suggests that it was caused by some humorally transported substance from the carcinoid tumor e g 5 HT

The findings are remarkable because the patient showed a complete carcinoid syndrome without any recognized deposits in the liver The signs and lesions of the carcinoid syndrome were believed to be due to the large size of the tumor and the high concentration of 5 HT in the tumor tissue the slow rate of growth evident from the long history and the fact that the tumor at least partially was drained directly into the caval vein without previous passage through the liver The immediate drop to normal of the previously consistently high 5 HIAA excretion and the clinical impression before and at surgery that all the tumor tissue was contained in the teratoid tumor agree with the finding in earlier cases that carcinoid deposits in ovarian teratoid tumors do not spread beyond the lining of the teratoid tumor

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THE ANTERIOR PITUITARY GLAND

Metabolic Effects of Human and Monkey Growth Hormone in Man were studied by John C Beck E E McGarry I Dyrenfurth and E H Venning[4] (Royal Victoria Hosp

(4) An I t Med 49 1090 1105 N v mbe 1958

survivors was 51 and average interval since treatment was 12 years Ten had severe or moderate changes of acromegaly without progression The hands and fingers of most patients had become thinner and more flexible and numbness of the hands and feet had disappeared The sella turcica showed no further changes in 15

One patient had had pronounced visual field changes be fore roentgen treatment These decreased rapidly during the following year and at follow up (21 years later) they were almost negligible These observations concur with other re ports that roentgen therapy can reduce the size of the hy pophysial adenoma and thus lessen the symptoms of pressure on the optic nerve

No optic nerve complications occurred during the later course of the disease

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NUTRITION AND LIPIDS

Six Month Evaluation of Anabolic Drug Norethandro lone in Underweight Persons I Weight Gain Although anabolic agents are potentially useful in clinical medicine the compounds heretofore available either have been inef fective or have undesirable side effects which preclude their prolonged use The anabolic effects of testosterone and its ability to increase appetite produce weight gain and induce a feeling of well being are well known However its andro genic action limits its clinical usefulness particularly in fe males and children

Norethandrolone (Nilevar®) (17α ethyl 17 hydroxynor androstenone) has been shown to be anabolic for both ani mals and man Animal experiments with this compound have shown an anabolic effect equal to testosterone but an androgenic effect only one sixteenth that of testosterone

Robert N Watson Matthew H Bradley Robert Callahan Bruno H Peters and Ross C Kory[6] (Marquette Univ) ad ministered daily for 12 weeks 1 oral tablet containing either a placebo or 25 or 50 mg norethandrolone to 54 volunteers using a double blind technic The subjects who received nor ethandrolone consistently demonstrated weight gains The

(6) Am J Med 26 38 4 F b y 1959

tention The second major influence seen with human and monkey growth hormone administration is the increase in urinary aldosterone excretion The third change is altera tion in carbohydrate tolerance seen with human and modi fied porcine growth hormone and occurring in all but 1 sub ject It can be postulated that these latter two phenomena are due to contaminants in the preparations used al though there is little evidence at present to suggest that the growth and diabetogenic principles of the pituitary are not identical

► [An additional effect of growth hormone in human beings is its ability to increase the concentration of nonesterified fatty acids in the plasma (Raben and Hollenberg J Clin Invest 38 484 1959) Results similar to those of Beck have been reported by Korner *et al* (Lancet 1 7 1959) —Ed]

Results of Roentgen Treatment of Acromegaly Clinical Review *Since 1920* the generally accepted treatment for acromegaly with optic nerve compression has been surgery possibly with subsequent irradiation and for all other cases roentgen irradiation only Bengt Arner Martin Lindgren and Bengt Lindqvist[5] (Univ Hosp Lund) reviewed data on 20 patients with acromegaly (1 with optic nerve com pression) treated during 1922 53 with x rays only

Average age at onset of disease was 35 Nineteen patients were first seen 1 9 years after onset the other had slight symptoms for 32 years Changes of acromegaly were pro nounced in 5 moderate in 14 and slight in 1 The sella turcica was appreciably enlarged in 11 None of the 20 had glycosuria or clinical signs of thyroid dysfunction Glucose tolerance was abnormal in 2 of 7 tested

The irradiation technic has undergone some modification during the period under study As a rule the hypophysis is now irradiated through two portals in each temple measur ing 4×4 cm Only one field a day is irradiated and treatment is continued for 3 4 weeks using 170 kv and a half value layer 0 9 mm Cu The tumor dose varied between 1 600 r/14 days and 4 200 r/27 days Size of the dose and degree and duration of the effect were directly related Ideally the dose should be 3 000 3 500 r/4 weeks

Of the 20 patients 4 had died before the follow up review 1 of tonsillar cancer 1 of cerebral hemorrhage 1 of acoustic tumor and 1 of cardiovascular disease Average age of the 16

(5) A t endocr of 29 575 586 Dec mbe 1958

dlesex Hosp Med School) with the assistance of Ivor Smith studied the effect on fat metabolism of urine collected from healthy persons during periods of fasting For comparison urine was obtained from the same persons on a normal mixed diet Batches of urine were collected and extracted in an identical manner and the extracts were injected into mice

The study showed that a substance or complex is present in the urine of healthy persons who have been fasting which on injection into mice increases the total amount of fat in the liver mobilizes fat from the fat depots appears to increase the total metabolic turnover of fat in the animals and causes weight loss without depressing appetite when given over a period the loss being in the form of body fat and water The active material was partially purified by paper chromatography The substance or complex cannot be detected in identical extracts made from urine of the same persons on a normal diet The substance called fat mobilizing substance seems to be present in the urine in certain conditions besides fasting associated with weight loss

► [We have a definite clinical impression that some patients tolerate fasting and severe caloric restriction less well than others Many of our obese patients become weak and nauseated after a 24 hour fast whereas nonobese control can tolerate up to a week of fasting without serious discomfort There are some indications that the inability to tolerate fasting may be associated with reduced ability to mobilize body fat stores Studies such as that of Chalmers may clarify the mechanisms of fat mobilization and perhaps ultimately provide agents which will promote the well being of obese patients whose diets are severely restricted in calories —Ed]

Problem of Fat Mobilization and Its Significance for Treatment of Obese Patients In all forms of experimental hyperlipemia with increased mobilization of fat from the depots acidosis develops simultaneously Intravenous injection of ammonium hydroxide produces increase of the fat content after a brief interval as a result of increased mobilization On the assumption that acidosis stimulates fat mobilization C D de Langen[8] (Utrecht) ascertained in a few cases of obesity whether the addition of ammonium chloride to a diet poor in calories had a favorable influence on the loss of weight

Woman 46 1 68 m tall and weighing 92 kg was placed on a diet of 1,250 calories daily consisting of about 100 Gm protein 100 Gm carbohydrates and 50 Gm fat In addition she took 4 Gm ammonium chloride daily For a few days she felt tired weak and somewhat dizzy

(8) G t oe t 1 g 83 109 118 1959

group receiving 25 mg gained an average of 5 5 lb and the group receiving 50 mg 4 7 lb The placebo group showed little change over the same period with an average weight gain of 0 3 lb The improvement in appetite reported by most subjects receiving norethandrolone was impressive Many had a voracious appetite while taking the drug

Undesirable effects were observed in 8 of the 10 females consisting of menorrhagia in 1 acne in 4 and amenorrhea in 7 The mechanism responsible for the amenorrhea is unknown These effects were more frequent on the 50 mg dose and were reversed by reducing the dosage or discontinuing the drug No hirsutism or changes in voice or libido were observed Drowsiness constipation and abdominal distress were observed as commonly in the placebo as in the norethandrolone group

Twenty five subjects who had gained weight while receiving the drug were observed for another 6 months after the drug was discontinued Nineteen maintained their weight or continued to gain Among the remaining 6 the greatest weight loss was 4 lb except in 1 man who lost 8 of the 16 lb gained while receiving norethandrolone The average weight loss in these 6 persons was only 0 7 lb /month

► [It seems likely that much of the effectiveness of this medication depends on its ability to increase the appetite The use of the double blind experimental technic however demonstrates that the effect is not purely psychogenic and that the drug produced more change than did placebos More studies of this type are needed in the difficult field of under and overnutrition —Ed]

Fat Mobilizing Activity of Human Urine Studies on obese persons have shown that if the calorie content of the diet is kept constant the rate of weight loss varies considerably with alterations in the composition of the diet Evidence also has suggested that the decrease in body weight could be accounted for by loss of body fat and water It appeared that a mechanism exists for controlling mobilization of depot fat that must be sensitive to changes in both composition and calorie content of the diet Such a mechanism should be operating at its maximum during fasting and if any hormonal agent is involved it should be detectable in the urine Indeed Weil and Stetten had already shown presence of a fat mobilizing substance in urine of fasting rabbits

T M Chalmers A Kekwick and G L S Pawan[7] (Mid

(7) La 1 1 866 867 Ap 26 1958

genesis produced by fat feeding may have resulted from a relative decrease in available insulin Experiments in which insulin treatment was given with fat feeding offered no support for this concept since fat synthesis was not restored

► [This study implies that a very low fat diet may be undesirable because it increases the synthesis of endogenous (i e saturated) fats Albrink has found that the plasma triglycerides may *rise* when some patients are placed on low fat diets (this YEAR BOOK p 696) —Ed.]

Effect on Human Serum Lipids of Dietary Fat Highly Unsaturated but Poor in Essential Fatty Acids Edward H Ahrens Jr Jules Hirsch Malcolm L Peterson William Insull Jr Wilhelm Stoffel John W Farquhar Theodore Miller and H J Thomasson[1] call attention to numerous studies which have shown that exchanges of dietary fats have striking effects on the concentration of lipids in the serum Thus unsaturated fats when substituted isocalorically for fats of more saturated types appear to produce definite decreases in the serum level of cholesterol and phospholipids Ahrens and co workers (1957) suggested previously that the effects observed are consistently related to the net unsaturation of the dietary fat But it has been postulated by others that serum lipid effects are due to the content of essential fatty acids in the dietary fat No specific fatty acid requirement has been demonstrated for the adult human but it is conceivable that hypercholesteremia in man might represent a biochemical expression of essential fatty acid deficiency Although it is important to distinguish clearly as to whether the serum lipid effects described are due to the essential fatty acid content of dietary fats or simply to net unsaturation this cannot be determined by feeding experiments with natural vegetable and animal fats However a partial answer might be obtained with the use of marine oils since these fats are highly unsaturated but reputedly poor in essential fatty acids

Fresh oil prepared from menhaden (Brevoortia tyrranus) and acceptable for human consumption in large quantities over a long period was used by the authors in dietary experiments in a metabolic ward The content of essential fatty acids in the oil determined chemically and by bioassay was found to be under 4% of the total fatty acids The content of total nonsaponifiable material was under 0 2%

When menhaden oil was substituted isocalorically for

(1) La t 1 115 119 J 17 1959

and was afraid that she would faint as during former reducing courses but these symptoms disappeared by the end of the 1st week After 14 days the daily quantity of ammonium chloride was lowered to 3 Gm After 1 month she had lost 5 kg This probably was not pure loss of fat as doubtless the ammonium chloride had also effected a fairly large loss of water She again lost 2 5 kg in the next month and continued to feel fit Subsequently the dose of ammonium chloride was lowered to 2 Gm daily and in each of the following 4 months she lost 2 5 kg When the diet was increased to 2 000 calories and ammonium chloride was omitted weight increased immediately and by the end of 2 weeks she had gained 1 5 kg Addition of 4 Gm ammonium chloride daily to the same diet stopped the increase but did not produce loss of weight The amount of calories was then reduced to 1 400 and ammonium chloride to 2 Gm daily The 1 5 kg the patient had gained disappeared in 1 month

► [It is difficult to be certain of the mode of action of ammonium chloride Perhaps its action is chiefly to reduce the appetite The previous study does not prove that ammonium chloride mobilized fat for this was not studied There is still plenty of room for further experimentation in this field —Ed]

Regulation of Hepatic Lipogenesis Influence of Dietary Fats was studied by R Hill Jose M Linazasoro François Chevallier and I L Chaikoff[9] (Univ of California) For 3 days rats received synthetic diets containing 0 1 2 5 5 10 and 15% fat The fats tested included lard corn and vegetable oil and hydrogenated vegetable oil The glucose content of each diet regardless of its fat content was kept constant at 50%

The livers of rats fed the diet devoid of fat had the highest capacity for converting acetate carbon to fatty acids A measurable depression in lipogenesis was observed when as little as 2 5% of fat was added to the diet When the fat content of the diet was increased to 15% the liver lost about 90% of its ability to convert acetate carbon to fatty acids All fats tested were effective in reducing hepatic lipogenesis Similar effects were observed when labeled glucose served as substrate These effects of ingested fat on hepatic lipogenesis occurred in the absence of changes in the glycogen and fat content of the liver and glucose and lipid content of plasma

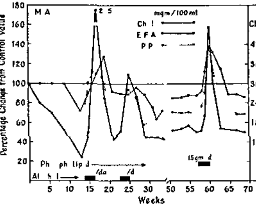
The mechanism by which feeding of fat depresses lipogenesis remains to be considered A diet rich in fat has been shown to lower the insulin content of the pancreas In view of the role of this hormone in carbohydrate utilization the authors considered the possibility that the depressed lipo

(9) J Biol Chem 231 305 310 Aug 1 1958

produced no change in total body weight and caused no gastrointestinal complaints

Results of the dietary tests appeared to confirm that the effects of the menhaden and corn oil on serum lipid levels were unrelated to the essential fatty acid and sterol contents of these fats

Dietary Control of Essential Hyperlipemia Effect of Dairy Foods Phospholipid Coconut Oil and Alcohol was studied by Donald S Amatuzio and Lyle J Hay (Univ of

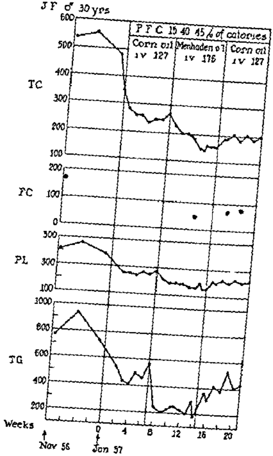


Fg 108—E p m t l d t w ma 45 w th g pect d k wn sent l hyp l pem f 5 y D t ted f 2 00 l w th 90 Gm f t da ly lud g d ry p od ct l h l d oc t ıl In 70 w k f tudy th w w ght g f 5 lb f m 129 lb N t ff ct f dd g l h l ph ph l p d (Court y f Am t D S nd H y L J A.M A A h I t M d. 102 173 178 A g t 1958)

Minnesota) in 9 patients previously recognized as having essential hyperlipemia No patient had a family history of essential hyperlipemia or hypercholesteremia Essential hyperlipemia has been described as a hereditary disease state of lipid metabolism The factors causing a sustained hyperlipemia are not known A decreased rate of removal of chylomicrons in essential hyperlipemia has been shown and may be due to inhibitory factors or a defect in lipid metabolism

After selective elimination of dairy foods coconut oil and alcohol from the diet of the study patients the fasting serum became clear with a return of all serum lipid components to normal values Body weight remained relatively constant or increased during the study No endocrine therapy was given

( ) A.M A A h I t Med. 10 173 178 Augu t 1958



F g 107 —S rum l p d h g n p t ent w th hyp l p m a utpat t a d wh n n th d ta y g m n n m tabol c n ad ll tum d et t tal chol t l FC f e h l te l PL ph ph l j d TC d t p ed as mg /100 ml rum d TG t gly d ll p ed d by t t pe od f 4 w k lod n valu E h n w t dy t te w La t l 115 l 19 J n 17 1959) (L rt y f Ab E H J t l

corn oil in the diet of 2 patients (1 with hyperlipemia the other with hypercholesteremia) the serum levels of cholesterol phospholipids and triglycerides remained depressed (Fig 107) The fatty acid patterns of all three ester groups of the serum lipids were considerably affected by the strikingly different composition of the two dietary fats Substitution of menhaden oil for the bland and relatively tasteless corn oil

suits H Gordon and J F Brock[3] (Univ of Cape Town) found that although there appears to be a characteristic level of serum cholesterol for the individual marked fluctuations around this level may occur from week to week The causes of these fluctuations are not always apparent

In 10 men long term effects of a dietary supplement of un saturated fat were studied In 8 of the 10 a significant de crease in the serum cholesterol level was produced the mean decrease for the whole group was 34 mg /100 ml After withdrawal of the unsaturated fat supplement the serum cholesterol usually returned to its former level In 5 of the 10 a second trial with a different unsaturated fat produced a similar effect In another 5 men under similar circumstances saturated fat supplements raised the serum cholesterol level significantly The fat supplements did not cause changes in body weight

The ingestion of added unsaturated fats is not recom mended The most practical cholesterol decreasing regime is one in which saturated dietary fats are moderately decreased and partly replaced by unsaturated fats

Practical Dietary Regime for Decreasing Serum Choles terol Level is presented by H Gordon and J F Brock[4] (Univ of Cape Town) In man the benefit of a cholesterol decreasing regime in relation to coronary heart disease has not yet been established Hence there is no indication for in troducing major changes in the eating habits of the commu nity as a whole but decreasing the serum cholesterol level may be important in certain instances such as the following patients with clinical evidence of coronary heart disease and serum cholesterol levels over 275 mg /100 ml persons with a strong family history of coronary heart disease and serum cholesterol levels over 275 mg patients with essential (fa milial or idiopathic) hypercholesteremia patients with in tractable angina pectoris or cardiac failure in whom artifi cial myxedema is induced and patients with diabetes mellitus with hypercholesteremia that does not respond to conven tional management of the underlying disease Since the fac tor in dietary fats that determines their effect on the serum cholesterol level has yet to be identified these indications are tentative only

(3) South Af M J 32 397-407 Ap 12 1958
(4) Ibid pp 907 911 S pt 13 1958

and no excessive exercise taken Restriction of other fats is not as important for the dietary control of hyperlipemia

The feeding of coconut oil or dairy foods will cause elevation of blood lipid levels without an increase of blood triglycerides in patients with hypercholesteremia These fats are highly saturated and also have a large quantity of short chain fatty acids The amount of fatty acids of chains of C^{14} or less in dairy products (milk, butter etc) and coconut oil is about 35 and 65% There is presumptive evidence that these two fats cause sustained hyperlipemia in patients with essential hyperlipemia

The addition of alcohol to the diet of the study patients was associated with sustained hyperlipemia (Fig 108) The feeding of egg phospholipid also produced hyperlipemia

It is generally accepted that on hydrolysis of fats in the alimentary tract the short chain fatty acids of 12 carbons and less are transported via the portal circulation to the liver and metabolized by this organ The fatty acids with less than 12 carbon atoms in the molecules are not stored in animal reserve fat even when fed in the diet Likewise the liver is the major site of oxidation of ethyl alcohol to water and acetic acid which is also a short chain fatty acid Because the liver is the site of metabolism of ethyl alcohol and short chain fatty acids essential hyperlipemia may represent a relative metabolic insufficiency or an increased state of lipid metabolism by the liver

Studies on Regulation of Serum Cholesterol Level in Man Serial Serum Cholesterol Determinations in Active Men on Their Ordinary Diets and Long Term Effect of Certain Saturated and Unsaturated Fat Supplements It has been established that the quality of a fat determines its effect on serum cholesterol levels in man It has been repeatedly confirmed that whereas certain saturated fats increase the serum cholesterol level some highly unsaturated fats decrease it However the effects of these fats have been demonstrated only in artificial circumstances viz in acute dietary experiments or with use of drastically modified or unnatural formula diets or in hospitalized patients on standardized diets

On investigating the effects of dietary fats for periods averaging 13 weeks in 30 men who ate their usual diets and continued with their usual business and recreational pur

triglycerides are turned over with great rapidity by heart tissue and that lipoprotein lipase occurs in high concentration in myocardial tissue

High triglycerides could not be attributed to dietary fat or excess calories Excluding patients studied during the first 8 days total calories were limited and fat restricted to 60 Gm a day or less in 24 of 45 male nondiabetic patients Triglycerides were elevated in 19 of the 24 cholesterol in 8 In certain persons an inverse relation between cholesterol and triglycerides was apparent after a low fat diet In these persons first the cholesterol declined somewhat but later the triglycerides rose markedly Others have reported similar increases in triglycerides in response to low fat high carbohydrate diets The treatment of coronary artery disease with low fat diets currently in common practice might in some instances raise the serum triglycerides an effect which might be undesirable

Effect of Certain Dietary Oils on Bile Acid Secretion and Serum Cholesterol Harry Lewis[6] (Univ of Cape Town) with the technical assistance of Enid Volks studied bile acid excretion during administration of various types of fat to 3 patients with complete bile fistulas

Hydrogenated coconut oil did not raise the serum cholesterol level and had no effect on composition of bile Sunflower seed oil given for 4 days lowered the serum cholesterol level significantly and produced fourfold increase in cholic acid secretion Desoxycholic acid and bile cholesterol output did not vary consistently The feces were virtually bile free Increase in cholic acid secretion began on the day the oil was introduced and thus preceded the fall in serum cholesterol levels (Fig 109) When sunflower seed oil was replaced by hydrogenated coconut oil the cholic acid secretion fell steeply but did not reach the basal level in 3 days Intravenous infusion of cotton seed oil was at least as effective as sunflower seed oil orally in lowering the serum cholesterol levels cholic acid output was increased

Quantitative considerations indicated that far more bile acid is produced during oil feeding than is necessary to account for the disappearance of cholesterol from the circulation The inference is that cholesterol is being mobilized from the tissues or more probably that cholesterol synthesis

(6) La t 1 1090 1092 M y 24 1958

In practice a conventional type of diet in which saturated fats (whole milk eggs butter bacon ham pork mutton cooking fats commercial pastry etc) are moderately restricted and partly replaced by unsaturated fats (cooking and salad oils cereals etc) is the most convenient method of reducing the serum cholesterol level Sample menus are presented

► *[The previous 4 papers are concerned with the effects of diet on the plasma lipids The data are consistent with the interpretation that on a constant fat intake unsaturation of the fatty acids of the diet will reduce plasma lipids however the nature of the unsaturated fats is less important than the fact that they are unsaturated. Moreover on a relatively low fat intake the plasma lipids are also reduced. Under these circumstances foods which are readily converted to fat (e g alcohol) may restore the plasma lipids to their pre diet level despite continuing restriction of fat intake*

The last 2 papers imply that simply adding extra unsaturated fats to the diet will reduce the plasma lipid concentration. However this is less successful than restricting the intake of saturated fats and replacing them in part with unsaturated lipids In other words unsaturated fats should not be used as a supplement but as a substitute for other dietary fats—Ed]

Serum Triglycerides in Coronary Artery Disease were studied by Margaret J Albrink and Evelyn B Man[5] (Yale Univ) Lipids are transported in serum as cholesterol and its esters phospholipids and triglycerides or neutral fat The authors studied the interrelations of these three major serum lipid fractions

Elevations of serum triglycerides above 5 5 mEq/L (about 160 mg/100 ml) occurred in only 5% of normal young adults in at most 30% of normal men over 50 and if the effects of acute illness were excluded in 85 90% of patients with coronary artery disease Few if any other lipid measurements that have been reported affect such a clear cut separation between normal and coronary subjects

An error in the metabolism of triglycerides is the lipid abnormality operative in coronary artery disease Other findings commonly reported in this disease such as increased cholesterol increased low density lipoproteins rich in triglycerides and prolonged and intensified alimentary lipemia may be secondary to decreased efficiency of triglyceride utilization with resulting accumulation of triglycerides in plasma It is tempting to speculate on the significance of these findings in relation to the energy metabolism of the heart particularly in the light of recent evidence that fat is an important source of fuel for the normal myocardium that

(5) A M A A h I t Med 103 4 B J a ry 1959

ceived 1 Gm buffered nicotinic acid (0 6 Gm sodium bicarbonate for each gram of acid) 3 times a day for 2 weeks The results showed that relatively large doses of buffered nicotinic acid decreased the serum cholesterol level in young healthy adults The decrease compares well with two previous tests on similar and partly identical groups in which unbuffered nicotinic acid was used Treatment with buffered nicotinic acid for 2 weeks lowered the mean cholesterol level for the 12 subjects from 201 4 to 161 7 mg /100 ml This difference is highly significant

When sodium intake should be kept low potassium bicarbonate can be substituted in any desired proportion for the sodium bicarbonate A practical preparation seems to be the following to 500 ml distilled water containing 32 Gm sodium bicarbonate (or 16 Gm $NaHCO_3$ and 16 Gm $KHCO_3$) is slowly added 50 Gm pure nicotinic acid preferably in a wide container to avoid overbubbling Of this solution 1 tablespoonful of 10 ml contains buffered nicotinic acid corresponding to 1 Gm pure nicotinic acid The best way to take this preparation seems to be 1 tablespoonful diluted in 1 glass of water after lunch and 2 tablespoonfuls in 1 glass of water after the evening meal

The high acidity rather than a specific action of nicotinic acid may be responsible for the occasional disturbances such as gastrointestinal reactions

► [The mechanism of nicotinic acid action is not yet clear Nausea vomiting and diarrhea are sometimes seen (Parsons and Flinn A M A Arch Int Med. 103 783 1959) which makes one wonder whether the effects of this drug may be a reflection of reduced caloric intake Parsons article says there was no change in weight among his subjects but the reduced carbohydrate tolerance observed by Gurian and Adlersberg (Am J M Sc. 237 12 1959) might be explained as a result of partial starvation The subject needs further study

Another interesting line of attack of hyperlipemia relates to the effect of low protein diets in increasing the plasma lipids (e.g Leveille and Fisher Proc Soc Exper Biol & Med 98 630 1958 Nath Harper and Elvehjem Arch Biochem 77 234 1958 Olson Diabetes 7 202 1958) If the caloric intake is kept constant a high fat diet necessarily contains less carbohydrate or less protein (or less of both) Some of the deleterious effects of high fat diets may therefore really be a result of the reduced protein intake—Ed]

Use of Intravenous Fat Emulsion in Management of Surgical Patients Paul H Jordan Jr[8] (Univ of California Los Angeles) reports results of a study of Lipomul® an improved fat emulsion administered in 323 nontherapeutic in

(8) A M A A h S g 76 794-806 M y 1958

is increased during administration of oil Increased synthesis from acetate has been demonstrated in liver slices from animals previously fed on cotton seed oil An analogy may be drawn with *hyperthyroidism in which there is a* tendency to a low serum cholesterol level despite increased cholesterol synthesis Animal experiments have shown that

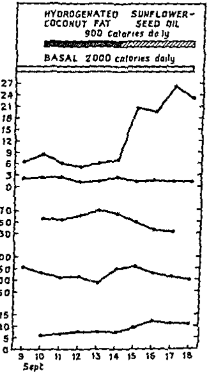


Fig. 109 —Response t hyd gen ted coc n t f t followed by s nfl wer seed l (Court y of Lew's B Lanc t 1 1090 1092 M y 24 1958)

thyroid hormone stimulates the degradation of cholesterol to acid derivatives

It is postulated that the mechanism by which the serum cholesterol is reduced by certain vegetable oils involves accelerated catabolism of cholesterol to cholic acid

Effects of Salts on Nicotinic Acid on Serum Cholesterol were investigated by *Rudolf Altschul and Abram Hoffer*[7] (Univ of Saskatchewan) Twelve university students re

(7) Brit. M J 2 713 714 Sept 0 1958

(Scrimshaw Taylor and Gordon Am J M Sc 237 367 1959) and the significance of nonesterified fatty acids in plasma (Dole A M A Arch Int Med 101 1005 1958) —Ed]

MISCELLANEOUS METABOLIC DISEASES

Porphyria in Sweden and South Africa Geoffrey Dean and H D Barnes[9] did quantitative determinations of δ aminolevulinic acid and porphobilinogen in urine and copro and protoporphyrin in feces on excreta from porphyric patients in Holland and Sweden and among white persons in South Africa

Porphyria seen in white South African patients did not fit well into the existing classifications Intermittent acute porphyria is a different genetic disorder from that which presents with acute episodes or cutaneous lesions and sometimes with both The name variegate porphyria is proposed for the latter

These two forms can be differentiated by several features (1) Cutaneous manifestations which are common in variegate porphyria are never seen in affected members of families with the intermittent acute form (2) In the latter excretion of porphobilinogen and δ aminolevulinic acid continues at a high level sometimes for years after the attack has subsided but in variegate porphyria it returns to normal or virtually normal levels as the patient recovers (3) Raised stool copro and protoporphyrin are characteristic of variegate porphyria even during remission from acute episodes and of latent cases without clinical manifestations In intermittent acute porphyria stool porphyrins may be slightly raised during the acute attack but are otherwise normal or nearly so

These biochemical findings indicate that in variegate porphyria the fundamental disturbance of porphyrin biosynthesis occurs at a later stage than in intermittent acute porphyria The precursors are satisfactorily transformed to the stage corresponding to copro and protoporphyrin and only then escape from the intracellular enzyme system This system is however sensitive to incidents such as the use of certain drugs which interfere at the δ aminolevulinic acid

(9) S th Afr M J 33 46-253 M 21 19 9

travenous infusions to 259 patients for the purpose of investigating the adverse effects associated with use of this emulsion after storage For most of the infusions 600 ml was used and was given at an average rate of 266 ml (40 Gm fat) an hour There was no appreciable difference in the number of reactions with fresh emulsion and with that stored for 18 months at 40 F and the febrile responses to Lipomul® stored under different conditions did not vary significantly

An additional 459 therapeutic infusions were done in 47 patients and 89% showed no reactions Infusions were discontinued in 6 patients because of chills and fever These symptoms were due to infection unrelated to fat emulsion in 2 patients and were of unknown cause in 4 Although blood lipid clearance studies and sulfobromophthalein evaluation have not been useful thus far in predicting onset of a reaction daily infusions of fat emulsion should be temporarily discontinued if the blood remains lipemic or if the sulfobromophthalein increases significantly Fat emulsion was not used in obese patients or in those with serious liver or collagen diseases

Metabolic data on 3 patients maintained on complete parenteral alimentation indicated that nitrogen equilibrium can be maintained for 15 days by this means The observation of a persistent negative potassium balance indicated that the potassium intake with a similar regimen should exceed the 40 mEq /day used in these studies

Two patients each of whom had bilateral operations at 1 month intervals received intravenous fat after the second operation and none after the first The data on these patients who acted as their own controls suggested that the nitrogen deficits incurred after surgery can be minimized by the addition of adequate nitrogen and calories to the intravenous diet

The data presented support the conviction that Lipomul® is safe for clinical use if administered with the ordinary caution usually afforded other types of medication Its use is indicated as a supplement to an inadequate oral diet in malnourished patients or as a high calorigenic material for complete parenteral alimentation over an extended period or for short periods during early convalescence after operation

► [A few important review articles should be mentioned These include a consideration of the clinical aspects of vitamin B deficiencies (Sebrell Am J Med. 25 673 1958) the interactions of nutrition and infection

(Scrimshaw Taylor and Gordon Am J M Sc 237 367 1959) and the significance of nonesterified fatty acids in plasma (Dole A M A Arch Int Med 101 1005 1958) —Ed]

MISCELLANEOUS METABOLIC DISEASES

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(9) S Afr M J 33 274-281 Mar 21 1959

and porphobilinogen stage and precipitate typical attacks of acute porphyria It is strongly recommended that a conservative attitude be adopted in the administration of drugs to patients in whom there is a possibility of porphyria and that barbiturates and sulfonamides be withheld from them

► [Classification of the congenital porphyrias has been a thorny problem. Dr Dean s experience with this disease in South Africa has led him to feel that previous functional classifications are unsatisfactory and that the disease should be classified on a genetic basis His recommendation probably stems from the fact that South African porphyria is a genetically homogeneous disease derived from a single afflicted immigrant who died in 1884 (Dean Semaine hop Paris vol 34 September 1958) I have asked Dr Cecil J Watson for his opinion of the matter and he has kindly written the following note

"The available evidence supports a primary separation of porphyria depending upon the principal site of the disturbance in porphyrin metabolism whether in relation to erythropoiesis in the developing red blood cells of the bone marrow the *erythropoietic form* or in the liver the *hepatic group* The former was described by Gunther as Porphyria Congenita but many cases classified under the latter term in the older literature undoubtedly belong in the hepatic group the confusion being due to the common photocutaneous lesions In the hepatic cutanea tarda cases in which the liver is rich in preformed porphyrin photosensitivity is usually first manifest in middle or later adult life in contrast to the erythropoietic cases in which it appears in infancy

Intermittent acute porphyria is the commonest form of the hepatic group There is some evidence of at least two genetically distinct forms of acute porphyria 1 The Swedish type (Waldenstrom) in which concurrent cutanea tarda disease is rare but has recently been observed 2 The South African type (Dean) in which acute and cutanea tarda varieties are usually encountered in the same families and sometimes in the same individuals thus constituting a mixed or combined type In the United States both types of families and individual cases have been observed There are also some families in which only porphyria cutanea tarda has been represented

"At the same time it is known that barbiturates may precipitate an acute attack in cases that would otherwise have been regarded as of pure cutanea tarda type

In mixed cases which may be more acute at one time and more photocutaneous at another the ratio of colorless precursor including porphobilinogen to preformed porphyrin in the liver has also been noted to change in relation to the patient s status porphyrin being more prominent with photosensitivity and vice versa With these considerations in mind the following subdivisions are warranted

"a Intermittent acute Example Swedish families
b Pure cutanea tarda (without acute manifestations)
c Mixed or combined (intermittent acute and cutanea tarda) in one family or one individual Example South African families

Further study is necessary to determine the exact nature of these differences and the extent to which they are genetically determined or related to factors of climate and environment

"The question of existence of an acquired or symptomatic porphyria cutanea tarda also requires further study The disease is much more frequent in chronic alcoholics but in the intermittent acute form attacks are also precipitated at times by alcohol It is reasonable to believe that what

has been called symptomatic or acquired porphyria cutanea tarda is a constitutional disturbance in which alcohol or liver injury associated with alcohol is an important precipitating factor

It appears to me that the present confusion is somewhat analogous to that which occurred in regard to defects of the clotting mechanism As the mechanics of clotting have been clarified the various deficiencies could be defined more clearly Present genetic theory would predict that ultimately all of the various types of congenital porphyria will prove to be the result of defects of one or more enzymes When the intermediary metabolism of the porphyrins and their precursors has been clarified and the defective enzymes identified the only logical classification will be an enzymatic (i.e. genetic) one At present our knowledge is not adequate for such a definitive classification, thus clinical criteria must be used to separate the various divisions of the disease —Ed.]

Studies on Biogenesis and Metabolism of Norepinephrine in Patients with Pheochromocytoma were conducted by Albert Sjoerdsma Lemuel C Leeper Luther L Terry and Sidney Udenfriend[1] (Nat l Inst of Health) The pathway for biosynthesis of norepinephrine in the body is now considered to be as shown in Figure 110 It has been shown in animals that phenylalanine C^{14} (which gives rise to tyrosine) tyrosine C^{14} 3 4-dihydroxyphenylalanine C^{14} (dopa) and dopamine C^{14} are precursors of adrenal norepinephrine and epinephrine It is usually assumed that the formation of norepinephrine precedes that of epinephrine

Chemical studies were made of 7 patients with pheochromocytoma Enzymes involved in the biogenesis and metabolism of norepinephrine were demonstrated in the tumors The 3 methoxy analogue of norepinephrine (normetanephrine) was found in each of 4 pheochromocytomas studied

It is believed the pathway for biosynthesis of norepinephrine in pheochromocytoma is the same as that shown previously in animal adrenal gland The chemical disorder in patients with this tumor may therefore be thought of as a disturbance in the metabolism of tyrosine Preliminary studies suggest that a lower fasting plasma tyrosine level may exist in these patients than in normals

Two reactions demonstrated in the biosynthesis of norepinephrine were the decarboxylation of dopa and the side chain hydroxylation of dopamine Other studies have shown that pheochromocytoma is more active in hydroxylating dopamine than are various animal tissues including adrenal gland Recent reports have indicated that some pheochromocytomas may produce dopamine as the predominant catecholamine Possibly some tumors produce only dopamine

(1) J Cl I t 38 (pt 1) 31 38 J uary 1959

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Normal Relatives of Patients with Wilson's Disease is reported by F C Neale and M Fischer Williams (Queen Elizabeth Hosp Birmingham England) The following biochemical abnormalities have been confirmed in patients with Wilson's disease increased content of copper in the liver brain and other tissues increased urinary excretion of copper decreased level of the copper in the serum and associated decreased level of copper containing plasma protein ceruloplasmin Other biochemical findings include aminoaciduria not necessarily with abnormal levels of amino acids in the blood This familial disease is inherited in a recessive autosomal way

Biochemical studies were made of 48 clinically normal relatives of patients with Wilson's disease The copper values obtained in the serum and urine in the relatives were compared with those found in 106 normal adults Urinary copper excretion was normal in all relatives The mean value for serum copper was 100 µg/100 ml in normal men and 108 µg/100 ml in normal women This sex difference is statistically significant On the basis of these control values 35 relatives showed normal serum copper levels Two child bearing relatives showed high values Of 11 asymptomatic relatives with low serum copper levels 5 showed levels that were undoubtedly abnormal (47 70 µg/100 ml) Since half of the relatives were beyond the age at which Wilson's disease manifests itself it may be concluded that some unaffected relatives have abnormally low serum copper levels

► [The use of chelating agents for treating Wilson's dis ase has improved the prognosis somewhat A review of the subject has been publ hed by Plattner (J Pediat 52 758 1958) The best of the chelating agent now available appears to be penicillamine (Walshe Brit M Bull 13 13 19 7 Am J Med 21 487 1956) —Ed]

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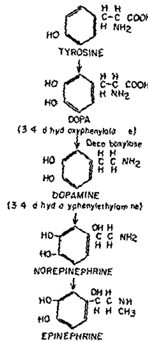


Fig 110 —Catecholamine pathway of tyrosine metabolism (Courtesy of Sjoerdsma A J Clin Invest 38 (pt 2) 3138 January 1959)

because of an inability to convert it to norepinephrine Since dopamine is a relatively weak pressor agent such a tumor might erroneously be termed nonfunctioning Further a dopamine producing tumor may not be detected by some of the bioassay and chemical procedures carried out on blood and urine A simple chemical assay on the tumor itself would reveal this

Estimations of norepinephrine turnover rate in 3 patients suggested a relatively short half life in some pheochromo cytomas as compared to animal adrenal glands The large pheochromocytomas probably originate from the adrenal gland and retain its properties of storage slow turnover and ability to produce epinephrine This may account for their growth to a much larger size before the amounts of cate cholamines which they secrete are sufficient to produce clin ical manife tations

Copper Metabolism in Normal Adults and in Clinically

INDEX

A

D

E

F

Q

R

S

T

INDEX TO AUTHORS